A domain-general perspective on medial frontal brain activity during performance monitoring

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General Abstract

Activity of the medial frontal cortex (MFC) has been implicated in attention regulation and performance monitoring. The MFC is thought to generate several event-related potential (ERPs) components, known as medial frontal negativities (MFNs), that are elicited when a behavioural response becomes difficult to control (e.g., following an error or shifting from a frequently executed response). The functional significance of MFNs has traditionally been interpreted in the context of the paradigm used to elicit a specific response, such as errors. In a series of studies, we consider the functional similarity of multiple MFC brain responses by designing novel performance monitoring tasks and exploiting advanced methods for electroencephalography (EEG) signal processing and robust estimation statistics for hypothesis testing. In study 1, we designed a response cueing task and used Independent Component Analysis (ICA) to show that the latent factors describing a MFN to stimuli that cued the potential need to inhibit a response on upcoming trials also accounted for medial frontal brain responses that occurred when individuals made a mistake or inhibited an incorrect response. It was also found that increases in theta occurred to each of these task events, and that the effects were evident at the group level and in single cases. In study 2, we replicated our method of classifying MFC activity to cues in our response task and showed again, using additional tasks, that error commission, response inhibition, and, to a lesser extent, the processing of performance feedback all elicited similar changes across MFNs and theta power. In the final study, we converted our response cueing paradigm into a saccade cueing task in order to examine the oscillatory dynamics of response preparation. We found that, compared to easy pro-saccades, successfully preparing a difficult anti-
saccadic response was characterized by an increase in MFC theta and the suppression of posterior alpha power prior to executing the eye movement. These findings align with a large body of literature on performance monitoring and ERPs, and indicate that MFNs, along with their signature in theta power, reflects the general process of controlling attention and adapting behaviour without the need to induce error commission, the inhibition of responses, or the presentation of negative feedback.

*Keywords*: medial frontal cortex; performance monitoring; theta power; independent component analysis; robust estimation statistics
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List of Abbreviations

ACC  Anterior Cingulate Cortex
ANOVA Analysis of Variance
BOLD Blood-Oxygen-Level-Dependent
CC  Certain to Certain
CI  Confidence Interval
CP  Certain to Possible
DLPFC Dorsolateral Prefrontal Cortex
ECG Electrocardiography
EEG Electroencephalography
EMG Electromyography
EOG Electrooculography
ERN Error-Related Negativity
ERP(s) Event-Related Potential(s)
ERSPs Event-Related Spectral Perturbations
FEF(s) Frontal Eye Field(s)
fMRI Functional Magnetic Resonance Imaging
FRN Feedback-Related Negativity
GFA Global Field Amplitude
IC(s) Independent Component(s)
ICA Independent Component Analysis
MEG Magnetoencephalography
MFC Medial Frontal Cortex
MFNs Medial Frontal Negativities
NoGo N2 Inhibitory N200
PC  Possible to Certain
PP  Possible to Possible
SHARCNet Shared Hierarchical Academic Research Computing Network
tDCS Transcranial Direct Current Stimulation
TMS Transcranial Magnetic Stimulation
Chapter 1

General Introduction

Extensive study during the past two decades has been focused on the role of the medial frontal cortex, including the anterior cingulate cortex (ACC), in performance monitoring and self-regulation, resulting in several proposals regarding how ACC structure and function provide a neural basis for the control of attention and behaviour. Early conceptualizations highlight the ACC’s contribution in biasing the allocation of attention for goal-directed behaviour (Mesulam, 1990; Posner, Fox, & Raichle, 1988), particularly with respect to coordinating and modifying behavioural response selection (e.g., ‘attention for action’; Posner & Dehaene, 1994; Posner & Petersen, 1990).

Similarly, more recent discussions in cognitive neuroscience focus on the associations between ACC activation and performance monitoring, evaluating, and adjusting behaviour vis-à-vis its role in modulating information flow between other brain regions (Paus, 2001; Posner, Rothbart, Sheese, & Tang, 2007; Weston, 2012). Although the core cognitive function of the human ACC has been variably attributed to paradigm-specific processes, such as error processing or response conflict, it is proposed here that the role of the medial frontal cortex in performance monitoring reflects a more general process of controlled attention modulation. This interpretation is supported by our data which suggests that a common factor accounts for medial frontal activation in various paradigms designed to focus on multiple neurocognitive processes, including error processing, inhibitory control, and processing external performance feedback.
Anatomical and clinical data implicating the medial frontal cortex and ACC in regulating attention toward task goals

Anatomically, the ACC is connected with frontal (lateral and dorsolateral, as well as primary, supplementary, and premotor cortices), subcortical (thalamus, amygdala, ventral striatum), and brainstem structures (locus coeruleus, monoamine nuclei, periaqueductal gray, red nucleus) known to mediate aspects of cognition, arousal, motivation, and intentional behaviour (Barbas & Pandya, 1989; Bates & Goldman-Rakic, 1993; Devinsky, Morrell, & Vogt, 1995; Dum & Strick, 1991; Paus, 2001; Vogt & Pandya, 1987; Vogt, Pandya, & Rosene, 1987). Given these connections the ACC can participate in the modulation of attention and facilitate changes in behaviour in the face of dynamic challenges (Medalla & Barbas, 2009; Paus, 2001; Weston, 2012). Clinical data also implicate the ACC in attention control as structural and functional disruptions often manifest as impairments in effortful and volitional attempts to regulate behaviour toward task goals, particularly when tasks are cognitively challenging and require rapid shifts in behaviour. Lesions to the ACC and surrounding prefrontal cortex have been associated with impairments in response control/inhibition and task switching in both human and non-human samples (Gläscher et al., 2012; Rudebeck et al., 2008; Rushworth, Hadland, Gaffan, & Passingham, 2003; Seamans, Floresco, & Phillips, 1995; Swick & Jovanovic, 2002; Swick & Turken, 2004), indicating that the ACC is involved in modulating attention toward task goals.

Animal studies on medial frontal cortex and ACC and controlled attention

Animal studies provides direct evidence that ACC activity is associated with attention control, task switching, and biasing behaviour toward task goals. Single-unit
recordings in rats show that commission errors reflect disorganized firing patterns (Lapish, Durstewitz, Chandler, & Seamans, 2008) of neuronal assemblies in the ACC and that associative learning and successful behaviour are underscored by the capacity to establish and maintain distinct functional relationships. Similarly, Bryden, Johnson, Tobia, Kashtelyan, and Roesch (2011) found that neurons in the rat ACC are sensitive to error commission, reward prediction errors, and become more active when there is an increased demand for attentional resources such as learning new response contingencies or during unexpected shifts in the value of a previously rewarded target. Indeed, the firing of neurons in the ACC are impacted by changes in task demands including task-switching (Johnston, Levin, Koval, & Everling, 2007), and events that inform optimal stimulus-response strategies (Quilodran, Rothé, & Procyk, 2008).

Neurons in the ACC of primates show enhanced phasic theta oscillations during both the preparatory and remedial stages of stimulus-response selections (Womelsdorf, Johnston, Vinck, & Everling, 2010a), again suggesting that the ACC is involved in establishing and modulating behavioural task-sets (Isomura, Ito, Akazawa, Nambu, & Takada, 2003). In addition, activation patterns of ACC neurons, as well as their functional relationship with other brain regions (Totah, Jackson, & Moghaddam, 2013), prior to the onset of stimuli are predictive of subsequent choice selection (Isomura et al., 2003; Womelsdorf et al., 2010a), particularly following a task switch (Johnston et al., 2007). These findings across species and paradigms are in line with a model of ACC function in which the ACC becomes engaged when task events demand increases or the maintenance of high levels of attention control so that task goals can be achieved.
The medial frontal cortex and performance monitoring

Different performance monitoring paradigms are used to examine attention, providing multiple lines of evidence, from ERP and functional magnetic resonance imaging (fMRI) studies, to suggest that ACC activity is affected by task demands. For example, amplitude of medial frontal ERP components and blood-oxygen-level-dependent (BOLD) responses increase when stimulus-response rules are reversed (Schroder, Moran, Moser, & Altmann, 2012) or when response conflicts, such as the need to shift responses to another stimulus dimension, are introduced (Hsieh & Wu, 2011; Liston, Matalon, Hare, Davidson, & Casey, 2006; Rushworth, Buckley, Behrens, Walton, & Bannerman, 2007). In addition, the size of MFNs (Randall & Smith, 2011) and ACC BOLD activity (Aarts, Roelofs, & van Turennout, 2008) are associated with changes in expectation, and relate to attention allocation in the pursuit of establishing appropriate response sets (Luks, Simpson, Feiwell, & Miller, 2002; Swainson et al., 2003), including biasing attention toward relevant stimuli when individuals attempt to minimize interference from task irrelevant information (Weissman, Gopalakrishnan, Hazlett, & Woldorff, 2005). Thus, task-switching and response shifts perturb ACC activity, suggesting that this brain region is recruited for coordinating and changing behavioural policies in order to achieve task goals (Woodward, Metzak, Meier, & Holroyd, 2008; Woodward, Ruff, & Ngan, 2006).

The sensitivity of the ACC to cognitive demands was validated by Paus (1998) who, after reviewing 107 PET studies, identified task difficulty as a key variable modulating activation in the ACC. Others have observed linear increases in ACC source activity as a function of response interference (Hanslmayr et al., 2008), and greater phasic
activation of the ACC when task demands require moment-to-moment adjustments in behaviour compared to when responses strategies need to be maintained (Wilk & Morton, 2012; Wilk, Ezekiel, & Morton, 2012). At the network level, functional connectivity within (caudal and anterior ACC) and between the ACC and frontal regions (dorsolateral prefrontal cortex, frontal operculum) is increased in cued conditions of a Go-NoGo task (Schulz, Bédard, Czarnecki, & Fan, 2011), suggesting that the ACC, along with other brain regions, coordinates processes related to preparing and/or biasing the selection of appropriate responses.

**Medial frontal cortex, medial frontal negativities, and controlled attention**

Several ERP components, including the error-related negativity (ERN), NoGo N200 (NoGo N2), and feedback-related negativity (FRN), have been attributed to the ACC’s role in error detection (Gehring, Goss, Coles, Meyer, & Donchin, 1993; Miltner, Braun, & Coles, 1997; Miltner, 2003), conflict monitoring and response control/suppression (Botvinick, Nystrom, Fissell, Carter, & Cohen, 1999; Nieuwenhuis, Yeung, van den Wildenberg, & Ridderinkhof, 2003; van Veen & Carter, 2002), feedback processing (Gehring & Willoughby, 2002), reinforcement/associative learning and error prediction (Holroyd & Coles, 2008; Holroyd & Yeung, 2012; Holroyd & Coles, 2002; Nieuwenhuis, Holroyd, Mol, & Coles, 2004), expectancy deviation (Oliveira, McDonald, & Goodman, 2007), and predicting the likelihood/timing of action outcomes (Alexander & Brown, 2011).

The ERN emerges following erroneous response commission and is elicited using speeded response tasks in which equally likely stimulus-response mappings occur on each trial, or responses need to be modified or inhibited. Unlike the response-locked
ERN, the NoGo N2 and FRN are locked to the onset of NoGo and feedback stimuli, respectively. Infrequent NoGo stimuli cue the need to withhold a pre-potent response and, when successful, individuals produce an enhanced negativity (approximately 200 to 350 ms) in the ERP compared to Go trials. The FRN is elicited to feedback stimuli informing individuals about response outcomes, particularly about whether or not a response was correct or their choices result in gain/reward or loss/punishment (Gehring & Willoughby, 2002). Researchers typically compute difference waves in order to isolate variance that is specific to response errors (ERN: Correct minus Error), conflict monitoring/inhibitory control (NoGo N2: Go minus NoGo), or feedback processing (FRN: Correct/Positive minus Incorrect/Negative). Collectively, these ERP components can be classified as medial frontal negativities (MFNs) on the basis of similar underlying neuronal generators and their topographic voltage distribution at the scalp, which consistently point to ACC and surrounding medial frontal sources (see van Noordt & Segalowitz, 2012).

Attributing the core function of the ACC to various paradigm-specific processes is tempting, in part because the described MFNs are elicited in different cognitive tasks. Although driven by different task events, a growing body of literature suggests that there is functional similarity across MFNs, not just in terms of scalp topographies (e.g., Gruendler, Ullsperger, & Huster, 2011), waveform morphology, and source generators, but that they can also be captured by the same latent component(s) in the EEG signal. Hoffmann and Falkenstein (2010) showed that the negative wave immediately following correct and error responses can be described by the same independent component (IC), whereas others have demonstrated overlap in cortical sources accounting for the
response-locked ERN and stimulus-locked FRN (Gentsch, Ullsperger, & Ullsperger, 2009). Extending these findings, Wessel, Danielmeier, Morton, and Ullsperger (2012) showed that the ERN and novelty N2, an ERP component elicited in response to infrequent task-relevant stimuli, also share common neuronal generators in the ACC and that the back-projected ERN independent components (ICs) can also describe the N2 response to novel stimuli.

It is obvious that the various MFNs are elicited under different experimental contexts and reflect, to some extent, different performance monitoring demands of the tasks. However, the medial frontal cortex response is not specific to error commission, conflict monitoring, response inhibition, or reinforcement learning. In addition to having similar cortical sources, each of these MFNs are similar in that they are affected by task demands to regulate or modify behaviour. These include bringing cognitive resources online when processing outcomes that inform behavioural choice selection, during feedback/reinforcement learning, or following the execution of an erroneous response. Thus, these brain responses are observed when a salient stimulus or behavioural event occurs, particularly when these events signal a need to change response patterns (e.g., when they involve a context switch cue, response conflict/inhibition, a behavioural error, or feedback processing). These findings have led several prominent researchers to suggest that these electrocortical signals reflect a realization of the need for cognitive control during performance monitoring (Cavanagh & Frank, 2014; Cavanagh, Zambrano-Vazquez, & Allen, 2012; Clayton, Yeung, & Cohen Kadosh, 2015; Hickey, Chelazzi, & Theeuwes, 2010; Narayanan, Cavanagh, Frank, & Laubach, 2013). This common theme suggests a simpler approach to describing and understanding the role of the medial
frontal cortex in attention control - i.e., effortful and volitionally engaged attempts to regulate awareness and behaviour toward task goals.

**MFNs, theta oscillations, and cognitive control**

Many researchers have moved beyond traditional ERP time-domain approaches and decompose the EEG signal, using short-time Fourier (Thakor & Tong, 2004) or wavelet transforms (Kumar, Sajeeth, Samar, Desjardins, & Segalowitz, 2014; Quiroga, Sakowitz, Basar, & Schurmann, 2001) to retain potentially important information about the spectral dynamics in the EEG. The practice of using a fixed-latency average amplitude approach permits the investigation of only partial phase alignment and changes in power driven by stimulus or response time locking (Le Van Quyen & Bragin, 2007; Sauseng et al., 2007). Not only do time-frequency transforms retain more of the EEG data, compared to the average voltage ERP approach, but they provide a more nuanced picture of brain dynamics and more closely reflect the activation of neuronal assemblies that generate scalp recorded EEG (Buzsáki, 2006). One measure that can be derived from time-frequency transforms is referred to as event-related spectral perturbations (ERSPs), which reflect changes in the mean EEG power that are driven by task stimuli or behavioural responses. ERSPs, unlike ERPs, are able to capture spontaneous changes in EEG power that are temporally stable but not coherent in phase angle across trials (Makeig, 1993; Makeig, Debener, Onton, & Delorme, 2004).

A literature focusing on the spectral properties of medial frontal activation during performance monitoring has exploded during the past decade. Within this literature there is a compelling consistency across studies illustrating that MFNs have a clear signature in theta rhythms (~ 3-8 Hz). Neurocognitive processes underlying response commission
errors, response control during conflict and inhibition, response cueing, and processing novel stimuli and unexpected/negative feedback have all been linked to transient peaks in theta power (Cavanagh, Frank, Klein, & Allen, 2010; Cavanagh et al., 2012; Cohen & Cavanagh, 2011; Cohen, Ridderinkhof, Haupt, Elger, & Fell, 2008; Hajihosseini & Holroyd, 2013; Luu, Tucker, & Makeig, 2004; Nigbur, Ivanova, & Stürmer, 2011; Trujillo & Allen, 2007). For example, researchers have found that theta power at medial frontal scalp sites increases following response errors (Luu et al., 2004; Trujillo & Allen, 2007), whereas others show that the presence of response conflict, such as those introduced by NoGo or flanking stimuli, also induce transient bursts of theta activity (Cohen & Cavanagh, 2011; Nigbur et al., 2011). Similarly, task outcomes that violate an individual's expectations are linked to increases in medial frontal theta power (Cavanagh et al., 2010). In addition to MFN ERPs in the EEG literature, convergence across fMRI, dipole source modeling, and MEG suggests that increases in theta power during performance monitoring are localized to cortical sources in the ACC and surrounding medial frontal regions (Asada, Fukuda, Tsunoda, Yamaguchi, & Tonoike, 1999; Cavanagh & Shackman, 2015; Hoffmann, Labrenz, & Beste, 2014; Ishii et al., 1999; Liu, Woltering, & Lewis, 2014; Tzur & Berger, 2007).

In addition to the general theme of increased medial frontal theta power following events that challenge behaviour and task goals, there is consistent evidence that these theta modulations reflect an important neural substrate for the adaptive control of behaviour in both human and non-human samples (Narayanan et al., 2013). In macaques and rats, theta is enhanced as a function of cognitive load (Tsujimoto, Shimazu, Isomura, & Sasaki, 2010), following task switches in stimulus-response rules (Johnston et al.,
2007; Womelsdorf et al., 2010a; Womelsdorf, Vinck, Leung, & Everling, 2010b), and has been shown to predict response outcomes prior to the onset of target cues (Womelsdorf et al., 2010a). In humans, theta is linked to the regulation of attention and behaviour, increasing when demands on response control are high (Cohen & Donner, 2013), following commission errors (van Driel, Ridderinkhof, Cohen, & Driel, 2012), and when individuals need to override habitual conditioned responses (Cavanagh, Eisenberg, Guitart-Masip, Huys, & Frank, 2013). Furthermore, theta power predicts behavioural shifts following unexpected outcomes (Cavanagh et al., 2010), post-error slowing (Cavanagh & Shackman, 2015), and response slowing between congruent and incongruent trials (Ma, Liu, & Chen, 2015). Together, frontal theta oscillations are thought to be a potential mechanism for the control of attention during action selection, feedback processing, and response shifts (see Cavanagh & Shackman, 2015; Cavanagh et al., 2012).

**ICA, robust estimation techniques and single subject statistics**

The application of independent component analysis (ICA) to derive latent factors that describe the projections of cortical sources has expanded during the past two decades. A major limitation of scalp recorded EEG is that the activity at scalp sensors reflects a mixed signal of the voltage projections from multiple brain regions that are simultaneously active. Because the spreading of field projections that occurs through volume conduction is relatively instantaneous, methods of blind source separation are necessary to isolate the independent contribution that various brain sources make to the scalp recorded EEG (Makeig, Bell, Jung, & Sejnowski, 1996). This method is therefore especially useful to isolate constituent brain processes in order to examine their relative
contribution to EEG and ERP components (Bell & Sejnowski, 1995; Debener, Makeig, Delorme, & Engel, 2005; Desjardins & Segalowitz, 2013; Hu, Mouraux, Hu, & Iannetti, 2010; Makeig et al., 1999). Compared to traditional processing and analysis of mixed scalp EEG, the use of ICA expands the types of questions and hypotheses that can be studied and provides better information about the unique brain dynamics of cortical sources (Delorme & Makeig, 2004; Makeig et al., 2004; Makeig & Onton, 2008).

Historically, psychologists have limited themselves to analyzing group averages with parametric tests. The field of cognitive and affective neuroscience, like many others, is no exception to this tradition. A host of issues can arise when relying on tests that assess differences in means and variances across groups (e.g., t-tests and Analysis of Variance), including the presence of group differences that misrepresent single subject effects. Moreover, the conventional approach to processing and scoring ERPs, along with the use of small sample sizes and data which likely violate model assumptions, can introduce additional theoretical limitations. Ultimately, conventional signal processing techniques coupled with parametric tests leads to an oversimplification of the data which, in turn, impairs our ability to understand the neural correlates of behaviour.

As with any statistical approach, parametric techniques are limited in their application. A central assumption of these tests is that sampling distributions reflect the normal curve. However, it is common for distributions to be asymmetrical, excessively kurtotic, and/or contain outliers (Wilcox & Keselman, 2003). For example, Wilcox and Keselman (2003) illustrate that sampling from data that are skewed creates appreciable incongruity between the actual t and normal distribution. Although this is especially problematic with small samples, the number of subjects needed to rectify these
discrepancies can easily become impractical (e.g., 200 to 300). In addition, outliers and uneven tails inflate the variance of the sampling distribution, thereby attenuating the $t$-statistic and reducing statistical power to reject the null hypothesis (Howell, 2009).

Ultimately, these issues lead to biased tests that can increase the likelihood of retaining a null hypothesis or, in other cases, they can produce exaggerated effect sizes (i.e., the likelihood of making a Type I error is not minimized in the presence of a true null hypothesis; Pernet, Sajda, & Rousselet, 2011; Rousselet, Husk, Bennett, & Sekuler, 2008; Rousselet & Pernet, 2011; Wilcox & Keselman, 2003). The repercussions of having poor measures of location and dispersion can manifest as unrepresentative confidence intervals, an alpha that is higher than the nominal level or is unequally divided between the tails of the distribution, and a reduction in statistical power for rejecting the null hypothesis (Wilcox & Keselman, 2003; Wilcox, 2005).

An alternative approach is to apply robust estimation techniques because these statistical measures and procedures are relatively insensitive to violations in model assumptions, such as non-normality, and are relatively insensitive to distribution characteristics, including skewness (Wilcox & Keselman, 2003; Wilcox, 2005). Applying robust estimation techniques is a way to deal with statistical limitations present in parametric tests, promote the retention of data for hypothesis testing, and permits the testing of hypotheses within individuals. ERP data do not escape the issues described above, and the conventional approach to processing ERP signals further constrains our understanding about the neural correlates of behaviour as reflected by intra-individual variability. The dominant strategy currently used in ERP research has methodological, statistical, and theoretical limitations. Although attempts are made to deal with complex
neurophysiological and behavioural phenomena, methods of signal processing and hypothesis testing oversimplify what is most likely true about the data (e.g., distribution characteristics), and what is certainly known to be true about the nature of brain function (e.g., simultaneous activation of multiple cortical regions and coordinated neural networks). Methodologically, EEG recordings result in extremely large amounts of data as a consequence of both the digitization of analog brain activity with high temporal resolution and high density electrode montages (data collected every 1-2 milliseconds across 128 different channels, resulting in 64,000 and 128,000 data points/second). It is clear that the process of averaging trials and scoring peak voltages dramatically reduces the data being used for analysis. Instead of examining voltages across all time points, both within and across trials, each subject’s brain activity is indexed by a single value reflecting peak voltage at a specific latency, at a single site, in a waveform that has been averaged across trials. These individual-level values are then typically averaged across individuals and compared between groups, or examined in terms of differences between individuals (i.e., inter-individual variance) and studied in relation to other individual differences variables.

Another concern, that can be resolved using robust estimation techniques, is that a large proportion of ERP studies include relatively small sample sizes. Many trials are collected for each individual and contained in group averages; however, effects are computed on sample sizes that rarely exceed 50 to 60 subjects, with most studies consisting of only a few dozen individuals. Aside from this deviation from the central limit theorem, there is no a priori reason to assume that ERP data are normally distributed, or that they conform to any other well defined distribution (Rousselet &
Pernet, 2011). It can be common for distributions of ERPs to contain outliers because the same neural processes can vary in appreciable magnitude across individuals, especially when captured as single peak voltages at specific scalp sites. Together, traditional processing and statistical analysis of ERP data can lead to situations in which there are large discrepancies between group averages and single subject averages.

These issues raise practical and theoretical concerns because they increase the likelihood of producing unreliable, non-replicable, misleading, or incorrect results which, in turn, directly impact interpretations regarding the functional significance of brain responses, or how these responses relate to behaviour. The standard method of scoring peak amplitudes at specific time points not only ignores the time-course of the neural oscillation, but it further implies that singular peaks in activity reflect a meaningful constituent of a particular neurocognitive process (Luck, 2005; Rousselet & Pernet, 2011). An alternative approach is to quantify differences in evoked responses across their entire time course. By doing so researchers retain the majority of their data and, in turn, can examine a more complete picture of brain activity within every individual studied.

Robust estimation procedures are not novel, but only recently have ERP researchers begun to apply some of these methods. Two major techniques of robust estimation include trimmed means and bootstrap re-sampling. One way to achieve a robust measure of location involves removing a certain percentage of cases from each tail of the distribution before calculating the mean. This technique, referred to as trimming the mean, has started to gain traction in recent ERP research (Desjardins & Segalowitz, 2013; Rousselet et al., 2008) and favours the central values of the distribution by minimizing the influence of unequal or heavy tails, either of which could drastically
affect the mean (Wilcox, 2005). Bootstrapping is a re-sampling procedure that is used to create distributions and obtain parameter estimates from existing data sets. The process involves sampling randomly, with replacement, $n$ times from an original pool of data to produce a bootstrapped sample and compute the parameter of interest (e.g., mean). Iterating this process several hundred or thousands of times creates a distribution of the estimated parameter and allows confidence intervals to be calculated. Null or alternative hypotheses can then be tested without making assumptions about the characteristics of the underlying distributions. Indeed, one of the main advantages is that bootstrap procedures are distribution-free, thereby ensuring that the validity of the test is not dependent on how the data are distributed. Several research groups have capitalized on the utility of these methods in different ways, such as examining how reliable well-established ERP effects are in individual subjects (Desjardins & Segalowitz, 2013; Rousselet et al., 2008; Rousselet & Pernet, 2011).

**Proposed Studies**

The overall goal of this dissertation is to examine the role of the medial frontal cortex in controlled attention by using novel response cueing tasks, advanced signal processing procedures, and analytical techniques of robust estimation for hypothesis testing. In a series of 3 independent studies we will examine whether medial frontal cortex activation during performance monitoring can be described from a domain-general perspective, focused on the need for increased attention control, as opposed to isolated and specific interpretations that focus on error processing, response conflict, inhibitory control, or reinforcement learning. In study 1, we isolate ICs, in single subjects, that represent medial frontal activation by using simple response cueing events and assess
whether these latent factors also describe traditional ERN and NoGo N2 ERP effects. In addition, we examine time-frequency transforms of the EEG data to test whether theta power is modulated as a function of cued response demands. Study 2 replicates and extends the functional classification of medial frontal activity from study 1 by using a shortened version of the response cueing task in a larger sample, and includes several commonly used performance monitoring paradigms. The inclusion of these additional tasks allows us to assess whether medial frontal ICs that are classified in the response cue task share a common neural signature in theta rhythms across multiple task events that signal the need for controlled attention (i.e., response-locked ERN, stimulus-locked N2, and stimulus-locked FRN). Furthermore, robust estimation techniques will be used to assess the reliability of medial frontal theta modulation within and between subjects. In study 3 we aim to expand our model by modifying our response cueing task to test whether medial frontal theta power is modulated during the preparation of controlled eye movement responses, as opposed to the traditional focus on activity evoked by stimulus or response outcomes.
References


Chapter 2

Watch out! Medial frontal cortex is activated by cues signaling potential changes in response demands

Published as:


Abstract

The human medial frontal cortex and especially the anterior cingulate cortex (ACC) have been implicated in several aspects of performance monitoring. We examined event-related EEG during a general process of controlling attention by using a novel paradigm to elicit a medial frontal negativity (MFN) to stimuli that indicate potential changes in future response demands. Independent Component Analysis revealed that the latent factors that accounted for MFN activity to such changes also accounted for activity associated with the error-related negativity and the NoGo inhibitory N2. Given that the medial frontal activation to these changes varied reliably across subjects simply as a function of potential need to alter responses in the absence of error commission and response inhibition, we propose that the underlying basis for medial frontal activation in situations demanding ongoing monitoring of performance involves an increase in attention control, a factor common to all MFN paradigms.
Introduction

One of the core cognitive functions of the human medial frontal cortex, in particular the anterior cingulate cortex (ACC), has been variably attributed to error detection (Gehring et al., 1993; Miltner et al., 1997), response-conflict monitoring (van Veen et al., 2001), reinforcement/associative learning (Holroyd & Coles, 2008; Holroyd & Yeung, 2012; Holroyd & Coles, 2002), deviation from expectancy (Oliveira et al., 2007), inhibitory control (Falkenstein et al., 1999), and the prediction of timing in action outcomes (Alexander & Brown, 2011). This range of models is due to the proliferation of paradigms that elicit a particular event-related potential (ERP) component, collectively referred to as medial frontal negativities (MFNs), which are thought to reflect activation of ACC and surrounding medial frontal sources. Functionally isolating and describing MFN effects such as the error-related negativity (ERN) and NoGo inhibitory N2 (N2) is complicated with respect to underlying neurophysiology, and tempered further by group-level statistics focused on mixed source projections in the EEG. We present evidence across single subjects that several MFNs are indeed functionally complicated, but can parsimoniously be attributed to the general process of controlling attention even in the absence of errors, response conflicts, reinforcement/associative learning, or inhibitory control. This general function can be shown to account for medial frontal activation that is typically associated with these paradigm-specific processes that result in the MFN.

Single-unit ACC recordings in rats suggest that functional relationships in neuronal assemblies serve as a basis for successful behavioral adaptation such that error commission reflects a lack of organization in firing patterns (Lapish et al., 2008). Extending this interpretation, Bryden et al. (2011) concluded that neurons in the rat ACC
are not only sensitive to commission and reward-prediction errors, but that they also become active when there is an increased demand for attentional resources such as those needed for the learning of new response contingencies or during unexpected shifts in target value. Indeed, the firing of neurons in the ACC is impacted by changes in task demands, such as task-switching (Johnston et al., 2007) and the presentation of events that inform optimal stimulus-response strategies (Hyafil et al., 2009; Quilodran et al., 2008). Some researchers have documented that phasic theta oscillations in the primate ACC increase during both the preparatory and remedial stages of stimulus-response selections (Womelsdorf et al., 2010), further suggesting that the ACC is involved in establishing and modulating behavioral strategies (Isomura et al., 2003).

In humans, activity in the ACC has been shown to increase when response conflicts are introduced (Hsieh & Wu, 2011; Liston et al., 2006) and when stimulus-response rules are reversed (Schroder et al., 2012). Others report that ACC activity, as reflected in a class of ERPs involving a MFN (Randall & Smith, 2011) and in blood-oxygen-level dependent (BOLD) responses (Aarts et al., 2008), is associated with changes in expectation and attention allocation in the pursuit of establishing appropriate response sets (Luks et al., 2002; Swainson et al., 2003). This includes biasing attention toward relevant stimuli in order to minimize behavioral interference in the presence of distracting information (Weissman et al., 2005). The ACC’s role in the dynamic online control of behavior is further reflected by data showing that phasic responses in the ACC are greater when task demands require moment-to-moment adjustments in behavior compared to when response strategies need to be maintained (Wilk et al., 2012).
Indeed, the medial frontal cortex is sensitive to cognitive load (Davis et al., 2005) and lesion studies involving both humans and rats show that medial frontal regions are important for the optimization of on-going behavior (Bissonette, Powell, & Roesch, 2013; Newman, Creer, & McGaughy, 2014; Sheth et al., 2012; Srinivasan et al., 2013). Several models focusing on error processing, response conflict, reinforcement learning, expectation violation, action-outcome predictions and evaluation (Jahn, Nee, Alexander, & Brown, 2014) explain well some empirical findings, but medial frontal activity is not necessarily specific to factors described in current models. For example, Grinband et al. (2011a, 2011b) show that medial frontal activity is modulated by time on task, irrespective of error likelihood or conflict stemming from competing response options. Others have reported that, compared to easier trials, simply showing individuals a preview of an upcoming trial that is relatively more difficult elicits MFN similar to those observed during error commission and inhibitory control (Oliveira, Hickey, & McDonald, 2014). Furthermore, functional connectivity within caudal and anterior regions of the ACC and between the ACC and frontal regions (dorsolateral prefrontal cortex, frontal operculum) is increased in cued inhibitory control conditions of a Go-NoGo task (Schulz et al., 2011), suggesting that the ACC, along with other brain regions, is involved in the coordination of those processes related to preparing and/or biasing the selection of appropriate responses.

Taken together, these data indicate that the role of the medial frontal cortex, including the ACC, in performance monitoring is not specific to error commission, response conflict monitoring, or reinforcement learning but might be better understood by focusing on what is constant across these various paradigms. A general theme regarding
medial frontal activation during performance monitoring is that the ACC and surrounding medial frontal cortex are sensitive to events that signal the need for changes in attentional and behavioral control. However, current data do not address the issue of whether the MFNs elicited in the various paradigms result from a common underlying generator and functional basis, or the degree to which these effects are reliable across subjects.

We present here data from a new paradigm demonstrating that an MFN ERP component is elicited when individuals are alerted to potential changes in response demands, and that this activation also describes MFN activity associated with the traditional ERN and response-inhibition NoGo N2. Importantly the MFN associated with stimuli signaling such a change in the response demands was not tied to processes based on error detection, response conflict, inhibition, reinforcement learning, or feedback evaluation and yet still accounted for the MFN resulting from some of these paradigms. Therefore, we propose that this basic function associated with the attention system reflects the underlying basis for medial frontal activation in situations that demand the dynamic ongoing monitoring of performance.

**Methods**

**Participants**

Twelve young adults ($M_{age} = 27$ years, $SD = 4.35$ years; 5 female, 7 male) participated in the present study, the majority of whom were university students ($n = 10$). Participants were free from any neurological or psychiatric conditions, and had self-reported normal or corrected-to-normal vision. Participation was voluntary and was not influenced by monetary compensation.
Task

Our novel task was similar to traditional NoGo paradigms in that the overall goal was to respond as quickly as possible to target Go stimuli and withhold responses to infrequent NoGo stimuli. The Go and NoGo stimuli were centered plus signs that were either black or white, counterbalanced across participants. The novel part of this task is that the Go and NoGo stimuli appear inside a square border, the color of which signaled the current context. The context border was always on the screen and changed color every 1 to 8 trials at the time of a Go stimulus onset. The context border indicated one of two situations: The “Certain” context indicated that the participant was in a run of trials consisting of only Go trials; the “Possible” context indicated that the run consisted of both Go and NoGo trials. Thus, participants knew whether or not there was a possibility of encountering NoGo trials and could use this information to adjust their response strategy accordingly. Each context was associated with a pair of colors, counterbalanced across participants. As an example, for half of the counterbalanced sessions a black or white border color indicated that there would be no NoGo trials (Certain run), but while the border was either red or blue a NoGo trial could occur on any trial (Possible run). Border color changes only occurred on Go trials. So, a border color change from black to white would indicate no change of context, but a border color change from black to red would indicate a change in context, say, from Certain to Possible. Thus, the border color changes were of four types: from Certain to Certain (CC), from Certain to Possible (CP), from Possible to Certain (PC), and from Possible to Possible (PP). Introducing these context cues allows us to assess whether changing expectations for Go versus NoGo trials is reflected in medial frontal activation. The task therefore consisted of seven types of
trials all together; four Go trials with a border color change (CC, CP, PC, and PP), two Go trials without a border change (Go in Certain context, Go in Possible context) and NoGo trials. Participants were given all the details regarding task dynamics and trial types, and could use this information to strategize behavior across contexts. See Figure 2.1 for a summary of the various Go and context cue trial types.

Figure 2.1 Schematic illustration of task parameters. Fixation crosses were presented for 50 ms followed by a 2 second response window. This example represents all stimuli features used in the task. Response context and response stimuli were counterbalanced across subjects.

Go and NoGo stimuli were presented for 50 ms and were followed by a 2-second response window, with an ITI selected randomly between 400 and 900 ms after the response. The task was performed in 4 blocks, approximately 12 minutes each, separated by short breaks. Participants completed a total of 2640 trials, which were broken down into the following trial types: 1776 Go trials without border color changes (888 x two response contexts: Certain and Possible), 576 with border color changes (144 x four types: CC, CP, PC and PP), and 288 NoGo trials.
Electrophysiological recordings and data reduction

Electrophysiological recordings were done using a 128-channel BioSemi Active Two system. The zero-reference principal voltage values (each site quantified relative to the driven right leg and common mode sense loop) were digitized at a rate of 512 Hz. Coordinates for the electrode montages were digitized for each subject using the Polhemus3 System® Fastrak. In addition to the 128 electrodes mounted in the cap, six external sensors were applied symmetrically on the zygomatic processes, outer canthi, and inferior orbital bones, as well as one sensor at the nasion.

Offline, automated pre-processing and bootstrap testing was done using EEGLab (Delorme & Makeig, 2004) with custom in-house code created in MATLAB 2010b and executed in Octave 3.6.3 on the Shared Hierarchical Academic Research Computing Network (SHARCNet). The data were systematically processed for the removal of bad channels and periods of non-stationarity based on correlation distributions between neighboring channels (see Desjardins & Segalowitz, 2013, for an expanded description of these methods). On average there were 12 channels ($SD = 6.54$, ranging from 5 to 28), before implementing independent component analysis (ICA). Extended infomax ICA (Bell & Sejnowski, 1995; Jung et al., 2001; Makeig et al., 2004) implemented in EEGLab was used to produce on average per subject 123 spatially fixed and temporally independent components (ICs). The activation values of the ICs were then used to classify periods of relative non-stationarity in the data. This was achieved by flagging periods of time in which 10% of the independent components had activation values that were outside of their own 99% confidence interval during in task periods of the recording (Desjardins & Segalowitz, 2013). Based on this criterion, on average 6% ($SD = 5.76$,
ranging from 2% to 22%) of in-task time was rejected. Following this rejection procedure, a second ICA decomposition was applied to the remaining time intervals. A single dipole was fit to the field projection weight matrix of each IC using the dipfit plugin for EEGLab (Oostenveld, Fries, Maris, & Schoffelen, 2011). Subsequent variance measures of IC activation (e.g., Global Field Amplitude (GFA) and percentage of variance accounted for) were calculated by taking the variance across channels, for each time point, once the IC activation was projected back to the scalp. For specific IC(s), back-projection to the scalp was accomplished by reducing the mixing matrix of the specific IC(s), which was then multiplied by the time course of activation for the IC(s).

Two levels of IC classification were used in this analysis. The first was the cortical classification and the second was the MFN classification. The goal of cortical classification was to reduce the EEG signal to all the cortical ICs (i.e., remove all non-cortical ICs). This cortically classified component set was then projected back to the scalp without ECG, EOG, EMG and other stationary noise sources, thus representing the full cleaned cortical EEG signal. The flagging of ICs as artifact was done initially on the basis of dipole residual variance. Specifically, those ICs whose field projections had a residual dipole variance of 15% or more were flagged for rejection. Subsequently, manual examination of the continuous signals and topographies was used as a final rejection criteria for biological (EMG, ECG or EOG) or channel artifact ICs. An average of 17 cortical components out of 123 per subject (on average) were retained in the cortical classification process. The MFN classification procedures followed the final data reduction procedure.
The final data reduction procedure in preparation for hypothesis testing included the purging of flagged time periods and artifact ICs. The cleaned continuous data were re-referenced to the average of 19 interpolated sites and filtered between 1 Hz and 30 Hz. The data were then segmented for the examination of various event-related measures. Response-locked trials were baseline corrected between -600 and -400 ms, and a baseline of -200 to 0 ms was used for all stimulus-locked trials. On average, individuals produced 69 error commission trials (response-locked for ERNs), 198 NoGo correct trials (stimulus-locked for MFNs), and 542 stimulus-locked border color change trials (137 CC, 137 CP, 132 PC, and 136 PP) that were artifact free.

Once the data were reduced for hypothesis testing, the MFN component classification was performed. From the cortically classified component data set for each participant, MFN component classification was accomplished by examining the spatial scalp variance at specific latencies in ERP condition differences (see Desjardins & Segalowitz, 2013). In the current study, this involved the comparison of stimulus-locked ERPs of correct border color change trials and the Go trials without a border color change. ICs were ranked by the percentage of variance accounted for in the difference topographies over the period associated with MFN activation. The period associated with the MFN activation was selected manually for each subject based on scalp data GFA (i.e., standard deviation of amplitude values across all channels at each time point) troughs on each side of the MFN peak. In Figure 2.2 this would correspond to the period between about 150 and 325 ms following the stimulus onset. The percentage of variance accounted for by a specific IC was calculated in the ERP difference between border change trials and Go trials in the Certain context averaged over the time period of
interest. This was the total spatial variance (all components projected back to the scalp) minus the variance of the other ICs (projected back to the scalp) divided by the total scalp variance. Components were added by order of their contribution in accounting for spatial variance in the GFA during the MFN on border color change trials minus Go trials until, cumulatively, they accounted for at least 60% of the spatial variance at the scalp (see Fig. 2.2). In one case the criteria had to be increased to 80% in order to include an MFN IC accounting for the border color change MFN effect. In cases where multiple ICs with various topographical projections were included in the 60% spatial variance criteria, manual selection of MFN ICs was used based on identifying a fronto-central medial topography. A single MFN IC was isolated for all participants with the exception of two individuals who had in addition a centrally projecting IC that accounted for scalp variance during the border color change MFN effect. The MFN-classified ICs had topographical projections similar to traditional ERN and NoGo N2 contrasts (see Figs. 2.5 and 2.7). A similar approach used by others focusing on the ERN has shown that, in most subjects, a single IC accounts for waveform differences between error and correct responses (Gentsch et al., 2009; Hoffmann & Falkenstein, 2010; Roger, Bénar, Vidal, Hasbroucq, & Burle, 2010; Silvetti, Nuñez Castellar, Roger, & Verguts, 2014; Wessel & Ullsperger, 2011).
Figure 2.2 Topographical maps of border change MFN IC back projections (left, black boxes) and residual data (right, red boxes) for border change and Go trials. Grand average topographies are shown in the top boxes, whereas individual topographies are shown in the bottom boxes. The shaded axis area (175 - 325 ms) highlights the latency window of the border change minus Go (e.g., stimulus N2) effect, which was used to classify MFN ICs and derive the topographical maps. The waveforms in the bottom panel show the global field amplitude of the difference between stimulus-locked border change and Go trials for the entire scalp data (green), MFN IC (black), and residual scalp data (red). Also shown are sLORETA source estimates of the cortical...
activation associated with MFN ICs (Brodmann Areas 6 [premotor and supplementary motor cortex], and dorsal 24 and 32 [anterior cingulate cortex]) and residual scalp data (Brodmann Areas 19 [extrastriate cortex], 22 [superior temporal gyrus], and 39 [angular gyrus]) between 175 and 325 ms.

**Statistical analyses**

**Robust estimation**

The hypothesis testing in the present study was performed using robust estimation techniques. Robust estimation refers to a class of measures that are relatively insensitive to distribution characteristic such as outliers, uneven tails, skewness, and to violations of parametric model assumptions (Wilcox, 2005). Conversely, parameters such as the arithmetic mean that are affected by distribution characteristics (e.g., outliers/extreme values) are considered non-robust estimators. There are several advantages to robust estimation, which include greater control over measures of location (e.g., the mean) and over unequally divided or inflated alpha levels, thus minimizing the likelihood of having unrepresentative confidence intervals and increasing statistical power for rejecting the null hypothesis. These techniques are especially useful in small sample sizes when there are no expectations of normality (as with ERPs), and for quantifying effects across the entire time-course of ERPs (Desjardins & Segalowitz, 2013; Rousselet et al., 2008; Rousselet & Pernet, 2011). Ultimately, these techniques provide greater control over Type I error and a better representation of the probability distribution.

In the present study, we used trimmed means for RT and electrophysiological distributions, and performed bootstrapping tests to assess differences across conditions. Trimmed means favor central values in a distribution and are calculated after removing a percentage of data points from each tail. In this paper, 20% refers to removing 20% of the values of the bottom and 20% of the values from the top of the ranked sample (leaving
the middle 60% of values) before calculating the mean. Bootstrapping is a re-sampling technique that allows one to obtain robust parameter estimates from a given surrogate distribution of size $n$. Sampling is done, with replacement from an original data pool to create a single bootstrapped (or surrogate) sample. For our purposes, a single bootstrapped surrogate sample reflects the difference, at each time point, between two categorical event related responses (e.g., border color change minus Go). For example, in the case of the GFA ERPs, given 100 artifact free trials in two conditions, 100 trials are selected randomly from each condition with replacement, the 20% trimmed mean (removing the top 20 and bottom 20 ranked values) is calculated for each condition, and then the difference value at each time point of the ERP GFA is stored as a single surrogate ERP. This process is iterated one thousand times to achieve a distribution of the estimated parameter (GFA ERP differences) and to calculate confidence intervals around the measure.

**Behavioral outcomes**

Given that task ITI was response-dependent, it is unlikely that very early responses belonged to a previous trial. These early responses more likely reflect anticipation of response execution, precisely what the task is meant to exploit during the Certain context. Nevertheless, to minimize carry-over of late responses from previous trials, response times faster than 50 ms and slower than 1000 ms were excluded. Single subject robust means are the average of 1000 surrogate means that were each calculated by re-sampling and then trimming by 20% the raw distribution of reaction times, thereby further stabilizing the means.
Analyses involving mean values were carried out using a robust ANOVA procedure that involves bootstrapping to assess differences between conditions. Specifically, a distribution of differences scores is established through re-sampling of the raw data. The mean of these differences is calculated after trimming the distribution by 20%. This bootstrapping of the raw data to create a distribution of difference scores, trimming, and mean calculation is repeated 1000 times. Follow-up pair-wise comparisons also implement bootstrapping to assess whether each contrast is significantly different from the null hypothesis. Similarly, we used a robust estimation technique for correlations in which paired values are re-sampled with replacement to create surrogate 'x' and 'y' distributions. Iterating this process 1000 times provides a robust measure of the correlation and as well confidence intervals.

Event-related potentials and time-frequency analyses

Each contrast was performed using the 20% trimmed mean of the trials, and included 1000 bootstrap samples. The 99% confidence interval was used to assess significant differences in the waveforms between -200 and 800 ms for stimulus-locked trials and between -600 and 800 ms for response-locked trials. To ensure comparable trial numbers in the averaged ERP global field amplitude (GFA), a maximum of 50 trials were used in each bootstrapped (or surrogate) sample for traditional Error minus Correct and Go minus NoGo contrasts (as the number of errors and NoGo trials are relatively limited); border color change minus Go contrasts used a maximum of 200 trials each. For the border color change condition, there were at least 111 trials available for bootstrap re-sampling. We examined the results for bootstrapping output when comparing border color change to Go trials on the basis of sampling 111 versus 200 trials and verified they...
were the same. This process of calculating the difference wave was iterated 1000 times for each categorical ERP contrast, and single-subject bootstrapped effects for functionally classified MFN-ICs are shown to demonstrate reliability in magnitude and timing across individuals.

The same bootstrapping approach was taken to assess the average event-related non-phase-locked spectral power in the theta frequency for border color change and Go trials across individuals. The time-frequency decomposition was achieved using the 'newtimef' function in EEGLab. Specifically, complex Morlet wavelets were used to convolve the event-related activity into spectral power for oscillations ranging from 3 to 30 Hz, with wavelet cycles increasing from 1 at the lowest frequency (3 Hz) to 14.5 at the highest frequency (30 Hz). Given that medial frontal theta band responses reflect a common neural signature of performance monitoring ERPs and cognitive control (Cavanagh & Frank, 2014; Cavanagh, Zambrano-Vazques, & Allen, 2012), we focused on theta band responses and used the bootstrapped z-scores for border color change minus Go contrasts and assessed differences against the 99% confidence interval.

**Results**

**Behavioral measures**

**Accuracy**

Response accuracy for Go trials (ranging from .96 to .99) and border color change trials (ranging from .88 to .99) were near ceiling levels whereas NoGo trial accuracy was considerably lower ($M = .72$, $SD = .10$) and variable (.52 to .93). Response accuracy varied between Go (in Certain and Possible contexts) and NoGo trials (omnibus test, $P$
Response times were significantly different across border change trial types (omnibus test, \( P = .038 \), one-way repeated measures robust ANOVA). Follow-up tests indicated that response times on PP trials were slower compared to PC trials (\( P = .004 \), robust \( t \) test), CC (\( P = .014 \), robust \( t \) test), and CP (\( P = .048 \), robust \( t \) test) trials. This shows that, across the four change types, individuals are slowest to respond on trials which cue the continuation of Possible NoGo trials (PP). Although no other pair-wise contrasts were reliable using our robust estimation approaches, it is worth noting that response times were slower when coming out of Possible (PC and PP) compared to the Certain (CP and CC) context (\( P = .041 \), robust \( t \) test) suggesting that individuals were sensitive to the response context as expected.

Response times also varied across Go and NoGo trials (omnibus test, \( P < .001 \), one-way repeated measures robust ANOVA). Specifically, average response times to Go trials were significantly faster in the Certain compared to the Possible context (\( P < .01 \), robust \( t \) test). In addition, responses made on NoGo trials (i.e., errors) were significantly faster than those on Go trials in the Possible context (\( P < .01 \), robust \( t \) test; see lines 6 and 7 in Table 2.1), with no reliable differences in response times between Go trials in the
Certain context and NoGo trials \((P = .09, \text{ robust } t \text{ test})\). See Table 2.1 for a summary of the descriptive statistics for response time across trial types.

**Table 2.1**
Robust means and standard deviations for response time and accuracy for Border Color Change, Go, and NoGo trials

<table>
<thead>
<tr>
<th>Trial Type</th>
<th>Response Time</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>SD</td>
</tr>
<tr>
<td>1. Border color change CC</td>
<td>253.26</td>
<td>8.47</td>
</tr>
<tr>
<td>2. Border color change CP</td>
<td>258.24</td>
<td>9.11</td>
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<tr>
<td>3. Border color change PC</td>
<td>264.21</td>
<td>7.90</td>
</tr>
<tr>
<td>4. Border color change PP</td>
<td>278.67</td>
<td>9.23</td>
</tr>
<tr>
<td>5. Go in Certain context</td>
<td>232.97</td>
<td>2.02</td>
</tr>
<tr>
<td>6. Go in Possible context</td>
<td>253.26</td>
<td>8.47</td>
</tr>
<tr>
<td>7. NoGo errors</td>
<td>227.43</td>
<td>5.45</td>
</tr>
</tbody>
</table>

To further assess the robustness of our experimental manipulation, we examined whether the difference in response times to Go trials across response contexts was statistically reliable within each participant. Taking advantage of the abundance of trials (approximately 700 per response context) we found that the effect was robust within subjects, indicating that every participant responded significantly more slowly to Go stimuli in the Possible compared the Certain context (see Fig. 2.3). Differences were considered significant when the standard deviation of the trimmed surrogate mean response time differences was greater than a \(z\)-score of 2.326 (i.e., 99% CI). These response time data indicate that all individuals were sensitive to the stimulus information, adopting a slower response strategy on Go trials when there was the possibility that the response would need to be inhibited.
Figure 2.3 Bar graph showing individuals’ robust mean response time to Go stimuli presented in Certain and Possible response contexts. Responses to Go stimuli were significantly slower in the Possible compared to the Certain context, at the group and single-subject level (all differences exceed the 99% confidence interval). Error bars reflect single subjects’ 99% confidence interval about the robust mean for each condition (i.e., single subject mean + [2.326 (single subject standard deviation of surrogates)]).

Individual differences

We also assessed individual differences in speed-accuracy trade-off as additional verification that our experimental manipulation affected task performance. This validation focused on the shift in response strategy to Go stimuli across contexts, and how this related to accuracy on NoGo trials. Our expectation was that greater shifts in response times (i.e., slowing down) between Go trials in the Certain and Possible context would be associated with better inhibitory control on NoGo trials because commission errors typically result from impulsive responses. Using a robust estimation approach we created a surrogate distribution of 1000 Pearson r coefficients and assessed significance in relation to the 95% confidence interval. Re-sampling for Pearson r in this case was done without trimming the distributions given the small sample size. Confirming our expectations, the mean difference in response time for Go trials (i.e., Possible minus Certain) was positively correlated with NoGo accuracy (robust, = .79, 95% CI [0.47
0.96]; see Fig. 2.4). These data illustrate that shifting to a slower response strategy in the Possible context is associated with a reduced propensity to make commission errors on NoGo trials.

![Figure 2.4 Scatterplot showing positive correlation between individuals' response time difference (i.e., response time to Go trials in Possible context minus response time to Go trials in Certain context) and NoGo accuracy. The shaded region surrounding the regression line indicates the upper and lower bounds of the 95% confidence interval.](image)

To ensure that the meaningful variance was specific to shifts in response strategy within subject and not to an individual difference in RT across subjects, we used the same robust Pearson r approach and correlated the RT difference score (i.e., Go Possible minus Go Certain) with (i) average RT on Go-Certain trials and (ii) average RT on Go-Possible trials. Neither of these relationships were statistically reliable (Ps > .25), indicating that the capacity to withhold prepotent responses was related specifically to the degree to which individuals adjusted responses and not general response speed.

**Electrophysiological measures**

*MFN Independent Components as related to response-locked ERN and NoGo N2*

**ERN.** Compared to correct responses, NoGo commission errors were associated with greater scalp GFA emerging at the time of button presses, continuing for 150 ms,
peaking at approximately 100 ms (see Fig. 2.5). In line with our expectations, the
difference activity during the time of the ERN was captured by the border-change MFN-
selected ICs, demonstrated in the bootstrapped $z$-scores that exceed 2.326 (Fig. 2.6). The
robustness of these findings are substantiated across individuals: for 11 of the 12 subjects,
their border-change MFN-selected IC accounted for differences between errors and
corrects within the first 150 ms following responses, i.e., accounted for the ERN.

**Figure 2.5** Grand average topographies of border change MFN IC (top-left, black box) and
residual data (top-right, red box) for Correct and Error trials. The shaded axis area (0 - 150 ms)
highlights the latency window of the Correct minus Error (i.e., ERN) effect, which was used to
derive the topographical maps. The waveforms show the GFA of the difference between
response-locked Correct and Error trials for the entire scalp data (green), border change MFN IC
(black), and residual scalp data (red).
Figure 2.6 Waveforms show the bootstrapped GFA for group ERP overlays of Error and Correct response-locked trials for the border change MFN-selected ICs (top) and residual scalp data (bottom). Significant differences in the categorical contrast are assessed in relation to the 99%
confidence interval (gray overlays), which do not include zero (horizontal red line). Between the overlays are single subject bootstrapped $z$-scores for the border change MFN ICs (top panel) and scalp residual (bottom panel). Plots are masked at the 99% confidence interval to highlight only those effects which are reliably different between conditions (i.e., $z$-score greater +/- 2.326). The tally bands indicate, at each time point, the percentage of subjects who demonstrate a reliable effect.

This pattern is further demonstrated in Supplementary Figure 2.1, which shows that the border-change MFN-selected ICs back-projected to site FCz captures the traditional error-versus-correct effect (black line Supplementary Figure 2.1e). The scalp GFA in Figure 2.5, waveforms for the $z$-scores in Figure 2.6, and site FCz indicate some effect in the residual scalp data during the ERN timing; however, it is clear from the residual topographical maps that this activation does not reflect a recognizable MFN (red line in Fig. 2.5). This is an important consideration, given that traditional scalp measures of the ERN can include residual effects that do not reflect medial frontal activation.

NoGo N2. As expected, there was greater activation in the MFN-selected ICs following NoGo compared to Go stimuli during the time of the N2, as reflected in both scalp GFA (green line in Fig. 2.7) and bootstrapped $z$-scores (Fig. 2.8). Similar to the ERN results, Supplementary Figure 2.1 further illustrates that the border-change MFN-selected ICs back-projected to the scalp reflect traditional stimulus-locked NoGo N2 effects at channel FCz (see black line in Supplementary Fig. 2.1f). These data show that MFN activity elicited by response cues can account for differences in activation between stimulus-locked correct Go and NoGo trials constituting the NoGo N2. Similar to the response-locked ERN effects, the scalp GFA in Figure 2.7, waveforms for the $z$-scores in Figure 2.8, and site FCz (Supplementary Fig. 2.1f) demonstrate effects in the residual scalp data that overlap in time considerably with the NoGo N2 effects. The topographies of these residual data show that this activity is not an MFN (Fig. 2.7). The single subject
data indicate that these effects are generally less reliable than those for the ERN, with only 6 of 12 individuals eliciting a MFN that accounts for the significant difference in N2 between the Go and NoGo trials, suggesting that the standard scalp NoGo N2 effect is a combination of mixed source projections, including some that are not medial frontal.

\[ \text{Grand average MFN IC topographical maps} \]

\[ \text{Grand average residual topographical maps} \]

\[ \text{Figure 2.7} \] Grand average topographies of border change MFN IC (bottom-left, black box) and residual data (bottom-right, red box) for Go and NoGo trials. The shaded axis area (175 - 325 ms) highlights the latency window of the Go minus NoGo (i.e., N2) effect, which was used to derive the topographical maps. The waveforms show the GFA amplitude of the difference between stimulus-locked Go and NoGo trials for the entire scalp data (green), border change MFN IC (black), and residual scalp data (red).
Waveforms show the bootstrapped GFA for group ERP overlays of NoGo and Go stimulus-locked trials for border change MFN-selected ICs (top) and residual scalp data (bottom). Significant differences in the categorical contrast are assessed in relation to the 99% confidence interval (gray overlays), which do not include zero (horizontal red line). Between the overlays are...
single subject bootstrapped z-scores for the border change MFN ICs (top panel) and scalp residual (bottom panel). Plots are masked at the 99% confidence interval to highlight only those effects which are reliably different between conditions (i.e., z-score greater +/- 2.326). The tally bands indicate, at each time point, the percentage of subjects who demonstrate a reliable effect.

**Independent Components and border-change-trial comparisons**

We compared, as a first step, activation between all four border-change trial types (CC, CP, PC, and PP) as a single condition with standard Go trials to identify a border-change N2 effect that could be captured by MFN-ICs. Subsequent analyses demonstrated that the border-change MFN-ICs can describe well the traditional ERN and NoGo N2 effects, although considerable variability exists across subjects. Given that the border color changes in our task signal different response demands, it is important to consider potential differences in activation as a function of the trial type and whether the effects are being driven by specific border changes. With respect to the 99% confidence interval (z +/- 2.326), bootstrap testing indicated border-change minus Go effects were reliable for each border-change type and are reflective of typical stimulus-locked N2 effects. Importantly, as there was no differentiation between border-change and Go trials prior to 240 ms, the border-change MFN-ICs are impervious to the changes in border color (in contrast to the evident P2 components) and therefore the border-change MFN-IC is predominantly sensitive to the cognitive demands signaled by the response cue (see Fig. 2.9).
Figure 2.9 Waveforms show the bootstrapped $z$-score ERP overlays of border change and Go trials for residual border change MFN-selected ICs (top) and scalp data (bottom). Significant differences in the categorical contrasts are assessed in relation to the 99% confidence interval (transparent overlays), which do not include zero (horizontal red line). The gray shaded axis areas highlight the time points where every border change trial type was differentiated from Go trials during the P2 (175 - 220 ms) and N2 (240 - 300 ms) latency ranges. Between the overlays are single subject bootstrapped $z$-scores for the border change MFN ICs comparing the difference between each border change trial type and Go trials. Plots are masked at the 99% confidence interval to highlight only those effects which are reliably different between conditions (i.e., $z$-score greater +/- 2.326). The tally bands indicate, at each time point, the percentage of subjects who demonstrate a reliable effect. Adjacent plots show differences in pair-wise comparisons.
between border change trial types, masked at the 99% confidence interval, for the border change MFN-ICs and scalp residual.

As can be seen in Figure 2.9, although border-change trials elicited greater P2 (approximate latency range of 165 to 200 ms) activation than Go trials, there were minor differences across border-change types only starting to emerge around 200 ms. This is also depicted by the pair-wise comparison plots showing the between-conditions bootstrapped z-score differences that exceed the 99% confidence interval. In clear contrast, z-scores of the border-change minus Go difference wave revealed a robust differentiation in MFN IC activity during the N2 (approximate latency range of 220 to 305 ms) that varied as a function of border-change type. The pair-wise comparisons of z-scores indicated that the GFA for PP trials was significantly larger than GFA on CC, PC, and CP trials. In addition, GFA was similar across CP and PC trials but was larger in both cases than GFA on CC trials (see Fig. 2.9 for summary). Together, these data show that the border-change MFN-selected ICs account specifically for the border-change N2 effect. In addition, these are associated with greater activation with CP cues signaling a greater need to increase vigilance than for the PP, PC or CC trials.

The single subjects' data complement well the overall findings at the group level. It is clear from the bootstrapped z-scores across individuals that results are not biased simply by the magnitude of effects in some individuals, but instead are driven by the number of subjects reliably differentiating between border-change and Go trials; larger differentiation between border-change and Go trials at the group level is a reflection of the consistency of effects across subjects. For example, PP trials signal the greatest level of response control that is required in the task and are most differentiated from Go trials, with 9 out of the 12 subjects reliably eliciting a MFN during the time of the N2.
Conversely, CC Switch trials signal the least demand on response control and are differentiated the least from Go trials, with only 5 of the 12 subjects showing a reliable MFN during the time of the N2.

Also demonstrated by the single subject data is the consistency in the timing of border-change N2 effects, as well as the nearly absent overlap between MFN and residual effects. For all four border-change minus Go contrasts, the subjects who demonstrate reliable effects do so within a considerably narrow time window between 250 and 300 ms. Thus, the MFN effects are tightly coupled around the time of stimulus-locked N2 ERPs. In addition, the time during the N2 is nearly fully captured by the selected border-change MFN-ICs with no effects in the residual. These data demonstrate not only that the MFN-ICs describe the border-change effects, but also that the timing of these N2 effects are highly stable across individuals unlike those found for the ERN and NoGo N2.

We examined further the differences in medial frontal activation to response cues by focusing on non-phased locked theta power. Overall, the border-change minus Go N2 effects observed in the ERPs are reflected in the oscillatory dynamics of the selected ICs, such that cues signaling the greatest demands on response control (CP and PP) are associated with more robust effects across individuals. A clear finding is the fact that border-change trial types differentiate from standard Go trials and group themselves based on the response context: moving into a Possible block (CP and PP) elicits similar responses, but are completely differentiated from trials moving into a Certain block (PC and CC) which themselves do not differ (see Fig. 2.10). Particularly striking in the time-frequency results is that the most robust differentiation across subjects is observed for CP
response cues, with all but one subject showing a reliable effect (the same individual who also showed unreliable effects in their ERP responses).

**Figure 2.10** Waveforms show the bootstrapped theta power z-score overlays of border change and Go trials for border change MFN-selected ICs (top). Significant differences in the categorical contrasts are assessed in relation to the 99% confidence interval (transparent overlays), which do not include zero (horizontal red line). The gray shaded axis areas highlight the peak effect for border change minus Go trials. Below the overlays are single subject bootstrapped z-scores for the theta power of border change MFN ICs comparing the difference between each border change
trial type and Go trials. Plots are masked at the 99% confidence interval to highlight only those effects which are reliably different between conditions (i.e., z-score greater +/- 2.326). The tally bands indicate, at each time point, the percentage of subjects who demonstrate a reliable effect. Adjacent plots show differences in pair-wise comparisons between theta power across border change trial types, masked at the 99% confidence interval, for the border change MFN-ICs.

**Discussion**

Medial frontal cortex function has been studied using a broad range of tasks and is thought to play a role in coordinating cognitive, affective, and behavioral processes across multiple contexts (Devinsky et al., 1995; Paus, 2001; Weston, 2012). Its role has been variously interpreted within the specific paradigm eliciting its activation and thus includes such processes as error-detection/likelihood, response conflict/monitoring, and response inhibition. We tested a simplified model of the controlled attention processes underlying all these effects and, through the use of a novel response-demand cueing paradigm, show that behavior and medial frontal activity are affected by stimulus cues signaling potential changes in response context that do not involve errors, response conflict resolution, or response inhibition. We successfully isolated, in each subject, medial frontal ICs accounting for variance in scalp GFA specifically during the time window of the stimulus-locked N2, and found that these ICs describe the variance in medial frontal activity in traditional response-locked ERN and stimulus-locked NoGo N2 contrasts. In addition, we found that the activation of these medial frontal ICs varied as a function of the type of border color change, being largest and most robust when the cognitive demands of the task were greatest. In addition to our ERP results, the non-phase locked theta band responses confirmed further the finding that MFN ICs are modulated by the demands signaled by the response cues, being largest and most differentiated from
Go trials when individuals are cued going into a context requiring dynamic response control (i.e., Possible) when coming from a context that does not (i.e., Certain).

Attributing the core cognitive function of the medial frontal cortex to various paradigm-specific processes derives, in part, from the fact that the medial frontal cortex and ACC generate different ERP components depending on the task event. However, a growing body of literature supports the notion that there is a functional equivalency across MFNs and that they can be captured by the same latent component(s) in the EEG signal without characterizing the functional nature of this commonality. Hoffmann and Falkenstein (2010) showed that the negative wave immediately following correct and error responses can be described by the same IC, whereas others have demonstrated overlap in the response-locked ERN and stimulus-locked FRN (Gentsch et al., 2009). In their study, Gruendler et al. (2011) collected ERNs, FRNs, and NoGo N2s and found significant overlap in their topographical scalp maps of peak activations across individuals. Using a different paradigm Wessel et al. (2012) showed that the ERN and novelty N2, an ERP component elicited in response to infrequent task-relevant stimuli, also share common neuronal generators in the medial frontal cortex and ACC and that the back-projected ERN ICs can also capture the medial frontal response to novel stimuli. We add to this literature by showing that simply presenting individuals with cues signaling the potential need for a relative increase in response control is sufficient to elicit an N2-like component whose IC can also describe the ERN and NoGo N2. Not only do our results converge with previous findings demonstrating functional overlap across MFNs, they also support a simpler model of medial frontal activation in performance
paradigms that differ in task demands but in which the modulation of controlled attention is the underlying principle.

The presence of a stimulus-locked N2 in response to border changes is not well described by some models that have been proposed to explain MFN effects in other tasks. With the exception of NoGo trials, each trial in the task required the same response with the only unique feature differentiating border-change trials from Go trials being a change in border color. The fact that response accuracy was at ceiling levels and undifferentiated across border-change and Go trials indicates that the modulation of medial frontal projecting ICs observed to border changes are not linked to error likelihood/expectancy or error commission, in addition to not being due to inhibitory control or performance feedback. It could be argued that the presence of the N2 on border-change trials reflects an expectancy violation due to their infrequent occurrence relative to standard Go trials. Although we do not disagree with this interpretation for the presence of an N2 to border-change trials generally, it is insufficient in explaining differences in activation across the different types of border-change trials, which occurred equally throughout the task. In regards to another proposal, Silvetti and colleagues have presented convincing evidence for overlap in the modulation of medial frontal activity in relation to cognitive demands or effort and reward expectation and prediction (Silvetti, Alexander, Verguts, & Brown, 2014; Silvetti, Nuñez Castellar, et al., 2014; Silvetti, Seurinck, & Verguts, 2011, 2013). Our findings are certainly compatible with some aspects of this model (e.g., prediction error signal evoked by infrequent border-change trials), but our paradigm is not focused on traditional aspects of reinforcement learning in which subjects are required to use external feedback to learn appropriate response contingencies or update behavioral
repertoires. Our paradigm required no learning about how to deal with task demands and offered no feedback about behavior, but simply offered cues that informed subjects about the potential need for dynamic response control.

Also demonstrated here is the reliability and consistency in effects across single subjects. This in-depth treatment of the data provides detail that may otherwise be inaccessible at the group level. For example, the 3 participants not showing a statistically reliable IC separation of PP and Go trials also produced poor ERNs and unreliable NoGo N2s. This is consistent with our conclusion that the border-change MFN-IC captures the core function resulting in the MFNs that make up the ERN and NoGo N2. Furthermore, our hypothesis predicts the exact timing and topography of the border-change MFN-IC effect, namely, a MFN during the N2. Thus, our results suggest a unifying function involving the modulation of controlled attention that accounts for medial frontal activation that has classically been interpreted in the context of paradigm-specific processes. These findings contribute to a growing literature presenting various theoretical perspectives that highlight the role of the medial frontal cortex in cognitive control.

The modified Go-NoGo task used here offers a way to elicit medial frontal activity to simple stimulus events which are, importantly, unrelated to error commission, stimulus-response conflict, response inhibition, explicit performance feedback, or unexpected feedback task events. Examining activation to simple stimulus changes avoids contamination from more complex task demands and cognitive processes (e.g., errors or response inhibition), and allows greater experimental control over the frequency, ordering, and variability of task events. In addition, having a task that maintains stimulus-response mappings ensures that differences in activation are due to
subtle implications of the stimulus content, not a result of proactive interference (e.g., previously learned associations interfering with current trial performance) or stimulus-response binding (e.g., interference resulting from changes in previous stimulus-response pairings). The combination of our ERP and time-frequency results indicate that medial frontal activation and the robustness of effects are modulated by the differences to the cues for the various response contexts. In particular theta band responses to CP trials were reliable in all but one subject (who was also atypical on other measures) and this cue most closely resembles (in our task) ERP events that are often used to study attention control (e.g., in ERN and NoGo paradigms). The border color change on CP trials signals the need to change from a ballistic response pattern to one that is more cautious, similar to how committing an error or receiving a NoGo cue signals the need to abort habitual responding. Thus, these data suggest that our task offers a way to study medial frontal activation on the basis of simple response cueing which is still compatible with more complex cognitive models. Our finding that MFN-ICs describe activation to cues informing individuals about the relative need for attention control fits well with the role of the medial frontal cortex in performance monitoring. Furthermore, by accounting for the ERN in error-detection and NoGo N2 in response inhibition paradigms, our results underscore the common need for attention control to appropriately resolve dynamic challenges to behavior.

Ultimately, our goal is to characterize and understand how the medial frontal cortex contributes to performance monitoring in conjunction with other brain regions. For example, the dorsolateral prefrontal cortex (DLPFC) has been identified as working together with the ACC in modulating attention and behavior (Gehring & Knight,
The ACC is connected with mid-PFC, DLPFC, and premotor regions (Bates & Goldman-Rakic, 1993; Devinsky et al., 1995; Paus, 2001; Petrides & Pandya, 1999) and several imaging and electrophysiological studies point to distinct, yet complementary, roles for these regions in controlled attention (Dove et al., 2000; Kerns, 2006; Liston et al., 2006; MacDonald et al., 2000). Researchers have also suggested that the ACC works together with the DLPFC to implement controlled attention (Schulz et al., 2011; Silton et al., 2010) and resolve interference from previously executed behavioral strategies (Hyafil et al., 2009); this is possibly through ACC inhibition of excitatory neurons in the DLPFC, thereby facilitating performance under conditions of high cognitive load (e.g., response selection, error process, and task-switching) (Medalla & Barbas, 2009). These interpretations converge with extensive clinical evidence pointing to the ACC and DLPFC as part of a key network mediating response and attention control in task switching (Gläscher et al., 2012). We suggest that attribution of a specific deficit in processes associated with a specific MFN-eliciting paradigm, such as error monitoring or response inhibition, may more parsimoniously be attributed to a general one of attention control. A potentially useful next step could be to isolate and map information flow across ICs attributable to ACC, DLFPC, and other cortical sources in order to better understanding the dynamic functional relationships between these regions that work together to support adaptive behavior.

Conclusions

We have demonstrated that simply alerting individuals to potential changes in response demands reliably affects task behavior and produces differential activation in ICs capturing MFN responses attributable to medial frontal sources. Importantly, medial
frontal activity related to this manipulation varied as a function of task demand in the absence of error commission, response conflict, inhibition, reinforcement learning, or feedback evaluation. Furthermore, traditional ERN and NoGo N2 effects were well explained by the ICs explaining border-change-related activity, supporting the interpretation that the medial frontal cortex responds to the general process of controlled attention modulation. Overall, our findings underscore the common need for attention control to appropriately resolve dynamic challenges to behavior and extend previous findings from the performance monitoring literature, suggesting that the broad role of the medial frontal cortex in attention control may be captured and clarified with simple response context paradigms such as ours.
Supplementary Figure 2.1 Top row: Waveforms at channel FCz for total scalp (green), border change MFN IC (black), and residual scalp (red) data for border change minus Go (left), Correct minus error (middle), and Go minus NoGo (right) contrasts. Solid lines represent border change, Error, and NoGo trials, whereas dashed lines represent Go, Correct, and Go trials. Bottom row: Difference waveforms at channel FCz between border change minus Go (left), Correct minus Error (middle), and Go minus NoGo (right) categorical ERP contrasts, for total scalp (green), border change MFN IC (black), and residual scalp (red) data. Note that the topographies of the residual of the Correct minus Error and Go minus NoGo differences do not indicate a medial frontal source, whereas the topographies of the border change MFN-selected ICs indicate a medial frontal source, shown in Fig. 2.5 and Fig. 2.7.
References


Chapter 3

Functional classification of medial frontal negativity event-related potentials: Theta power effects across tasks and within individuals

Submitted as:


Abstract

Theta oscillations in the EEG have been linked to several event-related potentials that are elicited during performance monitoring tasks, including the error-related negativity (ERN), NoGo N2, and the feedback-related negativity (FRN). We used a novel paradigm to isolate independent components (ICs) in single subjects' \( n = 27 \) EEG accounting for a medial frontal negativity (MFN) to response cue stimuli that signal a potential change in future response demands. Medial frontal projecting ICs that were sensitive to these response cues also described well the ERN, NoGo N2, and, to a lesser extent, FRN in Go-NoGo, Letter Flanker, and Time Estimations. In addition, bootstrap re-sampling of spectral power indicated that the medial frontal ICs show an increase in theta activity during the ERN, NoGo N2, and FRN effects across and within individuals. Our results provide an important validation of previous studies by showing that increases in medial frontal theta to cognitively challenging events is a robust effect within individuals, as well as accounting for events from the different performance monitoring tasks. Thus, medial frontal theta reflects a neural response common to all MFN paradigms and characterizes the general process of controlling attention without the need to induce error commission, inhibited responses or to present negative feedback.
Introduction

The medial frontal cortex, including the anterior cingulate cortex (ACC), is an important neural substrate for cognitive control (Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004). In the EEG literature, the functional significance of medial frontal cortex activity in the service of adaptive behavioural control and reinforcement learning is typically studied using event-related potentials (ERPs) that are generated in performance monitoring paradigms. Moving beyond the basic average amplitude and fixed latency ERP tradition, a growing body of evidence suggests that oscillations in the EEG offer a more nuanced understanding of canonical psychological processes and cognitive states (Makeig et al., 2004). In particular, the EEG dynamics reflected in medial frontal theta rhythms represent a common signature of cognitive processes that are engaged to challenging events (Cavanagh & Shackman, 2015; Cavanagh, Zambrano-Vazquez, & Allen, 2012; Cohen & Cavanagh, 2011; Hajhosseini & Holroyd, 2013; Holroyd & Yeung, 2012). Although there have been several elegant studies showing that theta-band activity in/over the medial frontal cortex is linked to cognitive control (Cavanagh & Shackman, 2015; Cavanagh et al., 2012), evidence is currently lacking that demonstrates the functional similarity of theta responses across different tasks or the extent to which effects are reliable within individuals. In the current study, we provide a thorough analysis for functionally classifying medial frontal activity using a novel response cueing task, show that latent factors in the EEG account for multiple brain responses across tasks, and that modulation of medial frontal theta is reliable within and between individuals.
Performance monitoring and medial frontal ERPs

From a cognitive neuroscience perspective, medial frontal function is often studied using performance monitoring tasks aimed at exploiting commission errors (Gehring et al., 1993), inhibitory control (Bokura, Yamaguchi, & Kobayashi, 2001), feedback-related learning (Holroyd & Coles, 2008; Holroyd & Yeung, 2012), response conflict (Carter & van Veen, 2007; van Veen, Cohen, Botvinick, Stenger, & Carter, 2001; van Veen & Carter, 2002), and task-switching (van Noordt, Desjardins, & Segalowitz, 2015a). Different functional neuroimaging methods suggest that medial frontal activation is sensitive to the cognitive demands of a task, typically increasing when task behaviour becomes more difficult to control due to trial unpredictability, competing stimulus-response associations, or the need to switch between different response strategies (Davis et al., 2005; Weissman et al., 2005; Wilk et al., 2012). With respect to the human EEG, a well known class of ERP components, collectively referred to as medial frontal negativities (MFNs), have been linked to medial frontal function and show similar source activations and topographical projections to the scalp during performance monitoring tasks (see van Noordt & Segalowitz, 2012). Some studies suggest that activation corresponding to different MFNs reflects a unifying function of the medial frontal cortex in the service of cognitive control. For example, several research groups have isolated independent components in the EEG which describe well a number of medial frontal ERP effects. The same latent factor describes negative deflections in the EEG following error and correct responses (Hoffmann & Falkenstein, 2010; Roger et al., 2010), error responses and feedback processing (Gentsch et al., 2009), as well as error responses and novelty N2 (Wessel et al., 2012). In our own lab, we have recently extended these
findings by demonstrating that medial frontal ICs accounting for activation to stimuli signaling potential changes in response demands also describe the scalp variance in traditional response-locked ERN and stimulus-locked NoGo N2 effects (van Noordt et al., 2015a). The functional similarity in these medial frontal activations during performance monitoring is bolstered further by the growing evidence that these ERPs have a common signature in theta rhythms.

**Performance monitoring and medial frontal theta**

Multiple neuroimaging methods, in both non-human and human samples, including functional magnetic resonance imaging (fMRI; Meltzer, Negishi, Mayes, & Constable, 2007), transcranial magnetic stimulation (TMS; Ott, Ullsperger, Jocham, Neumann, & Klein, 2011), magnetoencephalography (MEG; Ishii et al., 1999), and direct intracranial recordings (Cristofori et al., 2013; Isomura et al., 2003; Womelsdorf et al., 2010b), point to the ACC and surrounding medial cortical sources as generators of theta band responses during performance monitoring. In line with these findings there is much evidence that MFN ERP components elicited during performance monitoring oscillate in the theta range and are modulated by response conflict, punishment/unexpected feedback, error commission, stimulus novelty, inhibitory control, and response cueing (Cavanagh, Frank, Klein, & Allen, 2010; Cavanagh et al., 2012; Cohen & Cavanagh, 2011; Cohen, Ridderinkhof, Haupt, Elger, & Fell, 2008; Hajighosseini & Holroyd, 2013; Luu, Tucker, & Makeig, 2004; Nigbur et al., 2011; Trujillo & Allen, 2007; van Noordt et al., 2015a).

The functional significance of medial frontal theta is revealed by studies linking theta band activity to important aspects of cognitive control and performance monitoring. In macaques, theta is enhanced when attentional load increases (Tsujimoto et al., 2010)
and the patterns of theta oscillations in medial frontal neurons predict behavioural outcomes prior to the presentation of a target cue, particularly when stimulus-response rules need to adjusted (Womelsdorf et al., 2010a). Similarly, in humans, theta is an obvious neural correlate for the dynamic regulation of adaptive behaviour. Theta power increases when the demands on response control are high (Cohen & Donner, 2013), when individuals successfully override Pavlovian stimulus-response associations (Cavanagh et al., 2013), as well as following attentional lapses that result in commission errors (van Driel et al., 2012). Compared to poorer learners, frontal theta is greater in individuals who perform well in reinforcement learning contexts (Luft, Nolte, & Bhattacharya, 2013) and has been found to predict reaction time differences between congruent and incongruent stimuli (Ma et al., 2015), post-error response slowing/response switching (Cavanagh & Shackman, 2015), and behavioural shifts following unexpected outcomes (Cavanagh et al., 2010). Experimentally manipulating medial frontal cortex excitability systematically affects behaviour (Reinhart & Woodman, 2014), and greater theta phase synchrony is associated with improved response control following errors (Reinhart, Zhu, Park, & Woodman, 2015), which suggests that theta oscillations are essential to cognitive control. Taken together, electrophysiological performance monitoring studies implicate theta oscillations as a potential mechanism for the control of attention during action selection, feedback processing, and response shifts (see Cavanagh & Shackman, 2015; Cavanagh et al., 2012).

**Current study**

The first goal of the current study was to replicate our method of isolating latent factors in the single subjects' EEG that reflect medial frontal activation, specifically using
stimuli in our response cueing task that are not based on errors, response conflict, inhibition, or feedback processing. We show that medial frontal ICs classified in our response cue task also describe MFNs from other tasks. Importantly, the residual ERPs for the ERN, NoGo N2, and FRN do not reflect activity corresponding to traditional medial frontal sources. Finally, bootstrap re-sampling of time-frequency data shows that medial frontal theta effects are reliable both between and within subjects across several performance monitoring tasks.

**Methods**

**Participants**

Thirty young adults ($M_{age} = 24$ years, $SD = 7.34$ years; 21 female, 9 male) participated. These individuals self-reported normal or corrected-to-normal vision and that they were free from any neurological or psychiatric conditions. Compensation for participating included either $20$ honorarium or $2.5$ hours of research credit for qualifying courses. Data from three subjects were discarded from analyses due to excessive artifact and unreliable decomposition of their EEG into latent independent components. Thus, all behavioural and electrophysiological analyses were conducted on the remaining 27 participants. The study received clearance from the Brock University Bioscience Research Ethics Board and all participants provided informed consent.

**Tasks**

Each of the tasks in the current study used a dynamic adjustment in the speed of stimulus presentation so that task difficulty was sensitive to individual differences in speed and accuracy. This dynamic adjustment increases the likelihood of having a comparable level of difficulty across subjects, as opposed to having static parameters that
are insensitive to differences in individuals' capacity to perform the task. All four tasks 
were completed in approximately 45 to 60 minutes, depending on participant's response 
speed.

Response cueing task

The response cueing task used in this study is identical to the paradigm described 
in van Noordt et al. (2015a), with the exception that the total length of the task was 
truncated in order to accommodate the other three tasks. Similar to traditional NoGo 
tasks, the goal is to respond as quickly as possible to target Go stimuli and withhold 
responses to infrequent NoGo stimuli. The response stimulus was a plus sign that was 
black or white (counterbalanced across participants), the colour of which defined the trial 
as either Go or NoGo. The plus sign was presented inside a central square border that 
periodically changed colour, every 1 to 8 trials, simultaneously with the onset of a Go 
stimulus. The colour of the central square border indicated the current response context as 
either "Certain", a run of trials requiring only Go responses, or "Possible", a run of trials 
requiring both Go and NoGo responses. A pair of colours was associated with each of the 
response contexts. For example, a black or white border colour signaled the presence of 
only Go trials (i.e., "Certain" run), whereas red or blue border colour signaled that both 
Go and NoGo trials could occur (i.e., "Possible" run). These colour-contexts produced 
four response types including from Certain to Certain (CC), from Certain to Possible 
(CP), from Possible to Certain (PC), and from Possible to Possible (PP). The border 
colour change trials are important because they allow us to test whether medial frontal 
activation is sensitive to cues indicating potential changes in response demands, 
independent of errors, response inhibition, or processing performance feedback. All the
information about task goals, trial types, and colour-context associations were provided to participants. Thus, individuals did not need to learn these associations or task rules through trial-and-error, and instead could use the response cue information to modify their attention and behavioural control for optimal performance. See Figure 3.1 for a summary of the various Go and context cue trial types.

![Figure 3.1 Schematic illustration of task parameters. Fixation crosses were presented for 50 ms followed by a 2 second response window. This example represents all stimuli features used in the task. Response context and response stimuli were counterbalanced across subjects.](image)

Go and NoGo stimuli were presented for 50 ms and were followed by a 2-second response window, with an ITI selected randomly between 400 and 900 ms after the response. There were 660 trials in total, consisting of 68% Go trials (34% in the Certain and 34% in the Possible response contexts), 22% border colour change trials (5.5% for each of the four border colour change types), and 10% NoGo trials.
**Go-NoGo task**

A standard visual Go-NoGo task was used to capture the stimulus-locked NoGo N2 and response-locked ERN. In this task individuals responded to the rapid serial presentation of the letters 'M' and 'W'. One letter was designated as the "Go" target and requires a button press as quickly as possible, whereas the "NoGo" stimulus indicated that the response needed to be withheld. Target stimuli were counterbalanced across participants. There were 600 trials in total and a pre-potent response tendency was established by having 77% Go trials, 19% NoGo trials, and 4% repeated NoGo (i.e., NoGo trial following previous NoGo trial). Stimuli were presented for 50 ms. The ISI adjustment on trial \( n \) was based on a running tally of performance on the previous 10 trials, such that accuracy lower than 70% resulted in adding 15 ms to the ISI, whereas accuracy greater than 70% resulted in truncating the ISI by 15 ms. This adjustment reached a cap if the ISI was as low as 750 ms or as high as 1250 ms.

**Eriksen letter flanker task**

The Eriksen Flanker Task (Eriksen & Eriksen, 1974) is a well established performance monitoring task used to examine stimulus-response programming and the response-locked ERN. The participant's goal was to identify the central target item in a string of five letters and respond with the appropriate left/right button press. In this version the stimuli consisted of the letters 'H' and 'S'. Flanking letters introduce response interference when they are associated with the response opposite the central target letter (e.g., HHSHH, requiring left button press; incompatible), compared to when all letters are linked to the same response (e.g., HHHHH, requiring right button press; compatible). Stimulus-response mapping was counterbalanced across participants. The five letter
arrays were presented randomly for 200 ms. There were 660 trials in total, divided equally between congruent and incongruent trials. The ISI adjustment on trial $n$ was based on a running tally of performance on the previous 10 trials, such that accuracy lower than 70% resulted in adding 10 ms to the ISI, whereas accuracy greater than 70% resulting in truncating the ISI by 10 ms. This adjustment reached a cap if the ISI was as low as 500 ms or as high as 1250 ms.

**Time estimation task**

A time estimation task was used to collect FRNs to correct and error performance feedback. In this task, individuals were asked to make a button press when they thought that one second had elapsed following the disappearance of the trial cue. Feedback consisted of the words "Correct" or "Incorrect" depending on the accuracy of the response, but did not specify whether the responses were too short or too long. This allowed us to study feedback processing in the absence of rewards/punishments and reinforcement learning. Participants completed a total of 180 trials. Each trial involved a dynamic window within which responses would be deemed correct to increase the likelihood of comparable frequency across correct and error feedback. The initial window accepted responses as correct if they were delivered within +/- 100 ms of the one second interval. Subsequently, on trial $n$ the response window was adjusted by +/- 10 ms depending on whether or not subject's accuracy was at least 70% on the previous 10 trials. If accuracy was higher than 70% the window was truncated, whereas an accuracy lower than 70% resulted in the response window expanding.
**Electrophysiological recordings and data reduction**

EEG was recorded using a 128-channel BioSemi Active Two system. The zero-reference principal voltage values (each site quantified relative to the driven right leg and common mode sense loop) were digitized at a rate of 512 Hz. An average montage was used to represent the 3-D spatial location of channel coordinates. An additional seven external sensors were applied symmetrically on the zygomatic processes, outer canthi, and inferior orbital bones, as well as one sensor at the nasion.

Offline the EEG data were submitted to an automated pre-processing pipeline using EEGLab (Delorme & Makeig, 2004) with custom in-house code created in MATLAB 2010b and executed in Octave 3.6.3 on the Shared Hierarchical Academic Research Computing Network (SHARCNet). Specifically, the data were systematically processed to identify and remove bad channels and periods of non-stationarity on the basis of correlation distributions between neighbouring channels (see Desjardins & Segalowitz, 2013; van Noordt et al., 2015a; van Noordt, White, Wu, Mayes, & Crowley, 2015b, for an expanded description of these methods). There was an average of 19 channels (SD = 7.97, ranging from 3 to 37) removed before submitting the data to independent component analysis (ICA). Extended infomax ICA (Bell & Sejnowski, 1995; Jung et al., 2001; Makeig et al., 2004) was performed in EEGLab to produce spatially fixed and temporally independent components (ICs). The activation of these ICs was then used to identify and remove periods of time that showed relative non-stationarity in EEG. The flagging of time periods as unreliable was done if 10% of the ICs had activation values that were outside of their own 99% confidence interval during in-task time. After removing periods of time showing relative non-stationarity, a second ICA decomposition.
was applied to the remaining time intervals. Finally, using the dipfit plugin for EEGLab (Oostenveld et al., 2011), a single dipole was fit to the field projection weight matrix of each IC. Subsequent variance measures of IC activation (e.g., Global Field Amplitude (GFA) and percentage of variance accounted for) were calculated by taking the variance across channels, for each time point, once the IC activation was projected back to the scalp. For specific IC(s), back-projection to the scalp was accomplished by reducing the mixing matrix of the specific IC(s), which was then multiplied by the time course of activation for the IC(s).

Similar to van Noordt et al. (2015a), two levels of IC classification were used in this analysis. The first step was the classification of ICs as representing activation of cortical sources and the second step focused on classifying medial frontal projecting ICs. Cortical classification was done to remove all non-cortical ICs (i.e., ECG, EOG, EMG and other stationary noise sources) and reduce the EEG signal to only ICs that were likely to reflect the activity of cortical sources. Initially, ICs were flagged for rejection if the residual dipole variance was 15% and, subsequently by examining the continuous signals and topographies as a final rejection criteria for ICs representing biological or channel artifact. Across subjects an average of 10 cortical components were retained. The cleaned continuous data were re-referenced to the average of 19 interpolated sites and filtered between 1 Hz and 30 Hz for hypothesis testing. The continuous data were then segmented around task events of interest. Response-locked trials were baseline corrected between -600 and -400 ms, and a baseline of -200 to 0 ms was used for all stimulus-locked trials.
To isolate medial frontal projecting ICs for hypothesis testing, we examined in each participant the spatial scalp variance at specific latencies in the ERP difference between Go and Border colour change trials in the response cueing task (see van Noordt et al., 2015a). Specifically, we ranked ICs based on the percentage of variance accounted for in the ERP condition difference topographies over the period associated with stimulus-locked N2 effects (approximately 175 - 325 ms). Thus, the percentage of variance accounted for by a specific IC was calculated in the ERP difference between border change trials and Go trials in the Certain context averaged over the time period of the stimulus-locked N2. This was the total spatial variance (all components projected back to the scalp) minus the variance of the other ICs (projected back to the scalp) divided by the total scalp variance. Components were continuously added by the order of their contribution in accounting for spatial variance in the GFA during the N2 period on border colour change trials minus Go trials until, cumulatively, they accounted for at least 60% of the spatial variance at the scalp (see Fig. 2). In 7 cases the criterion had to be increased in order to include a medial frontal IC that was sensitive to the border colour change N2 effect (65% [n = 3], 75% [n = 1], 80% [n = 1], 85% [n = 1], 90% [n = 1]). If multiple ICs with various topographical projections were included in the spatial variance criterion, then manual selection of MFN ICs was used based on identifying a fronto-central medial topography. In 25 cases a single medial frontal projecting IC was isolated for each participant. There were 2 individuals who had 2 centrally projecting ICs that contributed to the scalp variance during the border colour change N2 effect. For these subjects the combined projection of the ICs were used to represent the medial frontal cluster. Both our lab (van Noordt et al., 2015a) and others (Gentsch et al., 2009;
Hoffmann & Falkenstein, 2010; Roger et al., 2010; Silvetti, Nuñez Castellar, et al., 2014; Wessel et al., 2012; Wessel & Ullsperger, 2011) have implemented a similar approach to classify medial frontal activity. Across these studies, a single medial frontal projecting IC is often found that accounts for waveform differences between categorical ERP contrasts that reflect common MFNs. Figure 3.2 summarizes the classification of medial frontal ICs across subjects for the Go versus border colour change trials, and clearly replicates the findings our previous study (see van Noordt et al., 2015a and Supplementary Figure 3.1).
Figure 3.2 Topographical maps of border change MFN IC back projections (left, black boxes) and residual data (right, red boxes) for border change and Go trials. Grand average dipole sources are shown in the top boxes, whereas individual topographies are shown in the bottom boxes. The shaded axis area (175 - 325 ms) highlights the latency window of the border change minus Go (e.g., stimulus N2) effect, which was used to classify MFN ICs and derive the topographical maps. The waveforms show the global field amplitude of the difference between stimulus-locked border change and Go trials for the entire scalp data (green), MFN ICs (black), and residual ICs (red). In order to maintain a clear visualization of voltage distributions, the topographies are
scaled within each subject, separately for medial frontal and residual ICs, based on the maximum voltages between Go and Border Colour Change trials. For example, medial frontal IC topographies for subject 1 are scaled based on the largest absolute values between Go and Border Colour Change trials. The same procedure is used for scaling the residual ICs for each subject.

**Statistical analyses**

*Robust estimation.* We use robust estimation statistics for hypothesis testing to examine the full time-course of ERP effects. The seminal work of Wilcox and colleagues (Wilcox & Keselman, 2003; Wilcox, 2005, 2009) has pioneered a class of robust estimation measures that are relatively insensitive to distribution characteristic such as outliers, uneven tails, skewness, and to violations of parametric model assumptions. Some of the advantages of using robust estimation techniques include greater control over unequally divided or inflated alpha levels, as well as more accurate measure of location such as the arithmetic mean. By using robust estimation the statistical power for rejecting the null hypothesis is increased by minimizing the calculation of unrepresentative confidence intervals. Ultimately, these techniques provide a better representation of the probability coverage and greater control over Type I error. Some researchers have successfully applied robust estimation techniques in EEG, and cognitive neuroscience research can benefit greatly from the use of robust estimation because sample sizes are often relatively small, there are no expectations of normality (as with ERPs), and effects can be quantified across the entire time-course (e.g., Desjardins & Segalowitz, 2013; Rousselet, Husk, Bennett, & Sekuler, 2008; Rousselet & Pernet, 2011; van Noordt et al., 2015a).

In this study, we used trimmed means instead of full means for both RT and electrophysiological distributions. The process of trimming, which favours central values in a distribution, is straightforward and involves removing a percentage of data points
from each tail before calculating the mean. The analyses in this study relied on trimming 20% of the values from the top and bottom (leaving the middle 60% of values) prior to calculating the mean. In addition to robust means, we also used bootstrap re-sampling to yield robust measure of significant differences between conditions. Bootstrapping involves re-sampling, with replacement, from an original data pool to create surrogate distributions. In this study a bootstrapped surrogate sample refers to the difference, at each time point, between a categorical contrast (e.g., border colour change minus Go).

For example, to assess spectral power differences, given n trials in each condition, 50 trials from each condition are selected randomly with replacement. The 20% trimmed mean (removing the top 20 and bottom 20 ranked trials) is calculated for each condition, and then the difference value at each time point is stored as a surrogate. Iterating this process 1000 times produces a distribution of the condition difference, for each time and frequency, and allows calculation of confidence intervals around the surrogate distributions.

**Behavioural outcomes.** To minimize carry-over of late responses from previous trials, or exceptionally slow responses, reaction times faster than 50 ms and slower than 800 ms were excluded for the Response Cueing, Go-NoGo, and Letter Flanker tasks. Robust means were used for response times, which reflect the average of 1000 surrogate means that were each calculated by re-sampling and then trimming each tail of the raw distribution by 20%, for each subject. Behavioural effects in this study were performed using a robust ANOVA procedure that involves bootstrapping to assess differences between conditions. Re-sampling of the raw data provides a distribution of differences scores, and the mean of these differences is calculated after trimming 20% of the values.
from both tails of the distribution. The bootstrapping of the raw data to create a
distribution of difference scores, trimming, and mean calculation is repeated 1000 times.

*Time-frequency analyses.* Event-related EEG activity was convolved, using
Morlet wavelets, into time-frequency spectrograms using the 'newtimef' function in
EEGlab. Spectral power from 3 to 20 Hz was calculated with wavelet cycles increasing
from 1 (at 3 Hz) to 8.5 (at 20 Hz). A standardized absolute z-score of 2.326 (i.e., 99%
confidence interval) was used to assess significant differences in spectral power between
-400 and 1000 ms for all trial types. To increase the likelihood of comparable trial
numbers in the averaged time-frequency spectrograms, we capped the trial numbers for
bootstrap re-sampling. All contrasts were capped at 50 trials, with the exception of the
correct versus repeat error in the Go-NoGo task, which was capped at 10 trials because
the occurrence of two successive NoGo trials was rare, resulting in a limited number of
trials available for re-sampling.

**Results**

**Behavioural measures**

**Accuracy**

The descriptive statistics for response accuracy across trials and tasks are
summarized in Table 3.1.
**Table 3.1**
Summary of descriptive statistics for response accuracy across tasks

<table>
<thead>
<tr>
<th>Task</th>
<th>Mean</th>
<th>Median</th>
<th>Mode</th>
<th>SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Response cue</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Go Certain</td>
<td>.95</td>
<td>.96</td>
<td>.99</td>
<td>.04</td>
<td>.84 - 1.00</td>
</tr>
<tr>
<td>Go Possible</td>
<td>.96</td>
<td>.97</td>
<td>.97</td>
<td>.06</td>
<td>.77 - 1.00</td>
</tr>
<tr>
<td>Border colour change CC</td>
<td>.96</td>
<td>.97</td>
<td>1.00</td>
<td>.06</td>
<td>.75 - 1.00</td>
</tr>
<tr>
<td>Border colour change CP</td>
<td>.91</td>
<td>.94</td>
<td>1.00</td>
<td>.10</td>
<td>.50 - 1.00</td>
</tr>
<tr>
<td>Border colour change PC</td>
<td>.93</td>
<td>.97</td>
<td>1.00</td>
<td>.13</td>
<td>.50 - 1.00</td>
</tr>
<tr>
<td>Border colour change PP</td>
<td>.93</td>
<td>1.00</td>
<td>1.00</td>
<td>.09</td>
<td>.58 - 1.00</td>
</tr>
<tr>
<td>NoGo</td>
<td>.71</td>
<td>.72</td>
<td>.72</td>
<td>.15</td>
<td>.39 - 1.00</td>
</tr>
<tr>
<td><strong>Go-NoGo</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Go Correct</td>
<td>.99</td>
<td>1.00</td>
<td>1.00</td>
<td>.02</td>
<td>.94 - 1.00</td>
</tr>
<tr>
<td>NoGo</td>
<td>.64</td>
<td>.62</td>
<td>.85</td>
<td>.15</td>
<td>.41 - .92</td>
</tr>
<tr>
<td>NoGo Repeat</td>
<td>.50</td>
<td>.50</td>
<td>.55</td>
<td>.20</td>
<td>.10 - .63</td>
</tr>
<tr>
<td><strong>Letter Flanker</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congruent</td>
<td>.88</td>
<td>.89</td>
<td>.86</td>
<td>.06</td>
<td>.79 - 1.00</td>
</tr>
<tr>
<td>Incongruent</td>
<td>.78</td>
<td>.77</td>
<td>.70</td>
<td>.08</td>
<td>.63 - .93</td>
</tr>
<tr>
<td><strong>Time Estimation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Correct</td>
<td>.53</td>
<td>.56</td>
<td>.57</td>
<td>.07</td>
<td>.36 - .63</td>
</tr>
</tbody>
</table>

Note: The near chance accuracy for border colour change trials CP, PC, and PP were due to one subject omitting responses on several trials throughout the task. Two other subjects showed some response omission on PP trials (one at .61 and one at .67), likely indicating an increased tendency to inhibit Go responses to potential upcoming NoGo stimuli. With the exception of these omissions, all other subjects responded correctly on at least 78% of trials.

**Response cueing task.** NoGo trials had lower and more variable accuracy scores across subjects, whereas response accuracy for Go and border colour change trials were near ceiling levels (omnibus test, \( p < .001 \)). Response accuracy was similar for Go trials between the Certain and Possible contexts (robust t-test, \( p > .05 \), 95% CI [-.02, .009]), and Go trials in both the Certain (robust t-test, \( p < .001 \), 95% CI [.02, .30]) and Possible (robust t-test, \( p < .001 \), 95% CI [.02, .30]) contexts were significantly higher than NoGo accuracy.

Although near ceiling levels, there was a reliable difference in response accuracy across border colour change trials (omnibus test, \( p < .001 \)). When coming from a Certain context where each trial is predictable, individuals tended to omit a greater number of
response on a border change trial that indicated the following block of trials was unpredictable (CP) compared to when the border change indicated that the following trials would still be predictable (CC; robust t-test, $p < .05$, 95% CI [.01, .07]). Similarly, commission accuracy was lower when individuals received a cue to change from habitual to dynamic responding (CP) compared to cues indicating that dynamic responding was still required in the following trials and no switch was required (PP; robust t-test, $p < .05$, 95% CI [-.65, -.01]). No other contrasts were statistically reliable. These results indicate that individuals were sensitive to response cues as they were more likely to omit a response to a cue indicating that they needed change their strategy to include the possibility of response inhibition on upcoming trials.

戈-诺戈任务。响应准确性在Go试次和标准（即，首次出现的NoGo试次）以及重复NoGo试次（完全检验，$p < .001$）之间存在差异。对比显示，Go试次的准确率高于标准（robust t-test, $p < .001$, 95% CI [.28, .43])和重复NoGo试次（robust t-test, $p < .001$, 95% CI [39, .59])。此外，响应准确性在首次NoGo试次相较于重复NoGo试次（robust t-test, $p < .001$, 95% CI [.05, .22])更高。

字母 flanker 任务。响应准确性作为试次类型的功能，与更高准确率对共轭相比不共轭试次（robust t-test, $p < .001$, 95% CI [.07, .12])。

响应时间

The descriptive statistics for response times across trials and tasks are summarized in Table 3.2.
Response cueing task. Response times varied across Go and NoGo trials (omnibus test, $p < .001$), such that responses on Go trials in the Certain context were significantly faster than Go trials in the Possible context (robust t-test, $p < .001$, 95% CI [-32.33, -19.07]), but similar to NoGo error response times (robust t-test, $p > .05$, 95% CI [-2.81, 13.06]). NoGo error responses were also significantly faster than responses on Go trials in the Possible context (robust t-test, $p < .001$, 95% CI [19.51, 35.85]). Focusing on the Possible context, which includes both Go and NoGo trials, we found that response times

Table 3.2
Summary of descriptive statistics for response times (ms) across tasks

<table>
<thead>
<tr>
<th>Task</th>
<th>Mean</th>
<th>Median</th>
<th>SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Response cue</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Go Certain</td>
<td>255.01</td>
<td>248.06</td>
<td>31.53</td>
<td>198.38 - 328.99</td>
</tr>
<tr>
<td>Go Possible</td>
<td>281.09</td>
<td>270.68</td>
<td>36.32</td>
<td>227.40 - 378.70</td>
</tr>
<tr>
<td>Border colour change CC</td>
<td>291.14</td>
<td>285.91</td>
<td>58.09</td>
<td>212.08 - 468.43</td>
</tr>
<tr>
<td>Border colour change CP</td>
<td>292.61</td>
<td>276.43</td>
<td>61.80</td>
<td>223.06 - 448.39</td>
</tr>
<tr>
<td>Border colour change PC</td>
<td>327.02</td>
<td>308.10</td>
<td>74.91</td>
<td>225.29 - 549.17</td>
</tr>
<tr>
<td>Border colour change PP</td>
<td>333.97</td>
<td>317.18</td>
<td>62.94</td>
<td>253.80 - 522.93</td>
</tr>
<tr>
<td>NoGo Error</td>
<td>251.85</td>
<td>238.98</td>
<td>34.85</td>
<td>207.52 - 359.74</td>
</tr>
<tr>
<td>Go Possible Pre-NoGo Error</td>
<td>279.56</td>
<td>271.30</td>
<td>35.96</td>
<td>227.83 - 370.94</td>
</tr>
<tr>
<td>Go Possible Post-NoGo Error</td>
<td>322.49</td>
<td>295.23</td>
<td>76.19</td>
<td>228.09 - 519.36</td>
</tr>
<tr>
<td><strong>Go-NoGo</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Go Correct</td>
<td>276.01</td>
<td>279.94</td>
<td>27.10</td>
<td>212.42 - 343.34</td>
</tr>
<tr>
<td>NoGo</td>
<td>233.77</td>
<td>234.93</td>
<td>23.14</td>
<td>184.60 - 284.03</td>
</tr>
<tr>
<td>NoGo Repeat</td>
<td>256.88</td>
<td>260.39</td>
<td>31.73</td>
<td>197.94 - 305.91</td>
</tr>
<tr>
<td>Go Correct Post-NoGo Error</td>
<td>338.56</td>
<td>344.24</td>
<td>48.87</td>
<td>251.20 - 431.73</td>
</tr>
<tr>
<td><strong>Letter Flanker</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Correct</td>
<td>407.75</td>
<td>416.38</td>
<td>50.44</td>
<td>271.86 - 493.37</td>
</tr>
<tr>
<td>Error</td>
<td>323.83</td>
<td>320.89</td>
<td>35.60</td>
<td>250.82 - 388.60</td>
</tr>
<tr>
<td>Congruent Correct</td>
<td>392.22</td>
<td>396.96</td>
<td>46.34</td>
<td>269.28 - 471.78</td>
</tr>
<tr>
<td>Congruent Error</td>
<td>312.38</td>
<td>317.34</td>
<td>39.21</td>
<td>241.05 - 396.63</td>
</tr>
<tr>
<td>Incongruent Correct</td>
<td>427.23</td>
<td>421.93</td>
<td>55.67</td>
<td>275.32 - 521.67</td>
</tr>
<tr>
<td>Incongruent Error</td>
<td>329.39</td>
<td>322.30</td>
<td>35.31</td>
<td>253.52 - 385.99</td>
</tr>
<tr>
<td><strong>Time Estimation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Correct</td>
<td>33.39</td>
<td>996.98</td>
<td>46.28</td>
<td>952.79 - 1134.35</td>
</tr>
<tr>
<td>Error</td>
<td>167.84</td>
<td>1053.90</td>
<td>206.06</td>
<td>539.53 - 1399.56</td>
</tr>
<tr>
<td>Correct Post-Error</td>
<td>38.43</td>
<td>1002.23</td>
<td>52.26</td>
<td>925.73 - 1167.99</td>
</tr>
</tbody>
</table>

Response times varied across Go and NoGo trials (omnibus test, $p < .001$), such that responses on Go trials in the Certain context were significantly faster than Go trials in the Possible context (robust t-test, $p < .001$, 95% CI [-32.33, -19.07]), but similar to NoGo error response times (robust t-test, $p > .05$, 95% CI [-2.81, 13.06]). NoGo error responses were also significantly faster than responses on Go trials in the Possible context (robust t-test, $p < .001$, 95% CI [19.51, 35.85]). Focusing on the Possible context, which includes both Go and NoGo trials, we found that response times

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on Go trials following an error were significantly slower than those preceding the error (robust t-test, $p < .001$, 95% CI [-62.34, -16.79]) as NoGo errors (robust t-test, $p < .001$, 95% CI [19.02, 35.02]). In addition, responses were significantly slower following an error compared to NoGo errors (robust t-test, $p < .001$, 95% CI [34.34, 87]). Together, these results indicate that errors are characterized by fast responses, with individuals being sensitive to the task demands by executing slower responses when there was a chance for NoGo trials, or slowing down following erroneous responses.

Response times also varied across border colour change trials (omnibus test, $p < .01$). Specifically, responses to Certain-Certain border colour changes were significantly faster than Possible-Certain (robust t-test, $p < .01$, 95% CI [-52.74, -14.45]) and Possible-Possible (robust t-test, $p < .001$, 95% CI [-65.32, -23]) border colour change trials. Responses to Certain-Possible border colour changes were significantly faster than Possible-Certain (robust t-test, $p < .001$, 95% CI [-47.06, -15.17]) and Possible-Possible (robust t-test, $p < .001$, 95% CI [-64.11, -20.37]) border colour change trials. There were no reliable differences between Certain-Certain and Certain-Possible border change trials (robust t-test, $p > .05$, 95% CI [-9.63, 12.65]), or between Possible-Certain and Possible-Possible border change trials (robust t-test, $p < .001$, 95% CI [-26.79, 5.82]). Together, these results indicate that individuals tended to have slower responses to border colour changes when coming out of a Possible context compared to a Certain context, suggesting that individuals were sensitive to the current blocked response context.

Go-NoGo task. Response times varied across Go and NoGo trials (omnibus test, $p < .001$). Specifically, correct responses were significantly faster than standard NoGo errors (robust t-test, $p < .001$, 95% CI [35.47, 47.32]), errors on repeated NoGo trials
(robust t-test, $p < .001$, 95% CI [7.66, 27.76]), and correct responses following a NoGo error (robust t-test, $p < .001$, 95% CI [-80.03, -45.26]). NoGo error responses were significantly faster than errors on repeated NoGo trials (robust t-test, $p < .001$, 95% CI [-34.39, -14.21]) and correct responses following NoGo errors (robust t-test, $p < .001$, 95% CI [-120.88, -86.62]). Finally, errors on repeated NoGo trials were significantly faster than correct responses following NoGo errors (robust t-test, $p < .001$, 95% CI [-95.29, -62.99]). Together, these results indicate that individuals were sensitive to task demands by slowing down when facing NoGo trials, even if errors were made on repeated NoGo trials, and adopting an even slower response strategy for Go trials following errors.

*Letter Flanker task.* In general, responses were significantly faster for error compared to correct trials (robust t-test, $p < .001$, 95% CI [70.20, 91.07]). There were also reliable differences for error and correct responses across trial type. Specifically, correct responses on congruent trials were significantly slower than congruent (robust t-test, $p < .001$, 95% CI [66.38, 91.24]) and incongruent errors (robust t-test, $p < .001$, 95% CI [48.64, 71.56]), but faster than incongruent correct responses (robust t-test, $p < .001$, 95% CI [-41.17, -27.61]). Responses on congruent errors were significantly faster than incongruent correct (robust t-test, $p < .01$, 95% CI [-131.25, -97.76]) and incongruent error trials (robust t-test, $p < .001$, 95% CI [-27.91, -5.94]). Finally, incongruent correct responses were significantly slower than incongruent error responses (robust t-test, $p < .001$, 95% CI [80.55, 108.77]). Together, these results indicate that individuals were sensitive to task demands such that responses on error trials were faster than correct responses, and responses on congruent trials were faster than responses involving incongruent flankers.
**Time Estimation task.** Time estimates varied across correct, error, and post-error trials (omnibus test, \( p < .05 \)) with respect to their absolute deviation from 1 second. Incorrect estimates showed a significant deviation from 1 second compared to correct (robust t-test, \( p < .001 \), 95% CI [-168.60, -77.21]) and post-error correct estimations (robust t-test, \( p < .001 \), 95% CI [76.92, 160.62]). The deviation from 1 second on correct trials was comparable to the deviation on post-error correct trials (robust t-test, \( p > .05 \), 95% CI [-15.20, 5.45]). Together, these results indicate that error trials were characterized by a larger deviation from 1 second estimates than correct trials.

**Medial frontal ICs as related to the NoGo N2, FRN, and ERN**

To assess whether MFN responses across paradigms are similar, we examined whether the medial frontal ICs that were classified in our response cueing task also describe the ERN, NoGo N2, and FRN from the other performance monitoring tasks. Figure 3.3 shows that traditional MFN effects are well described by the ICs that were classified to border color change trials in our response cueing task. Specifically, there is considerable overlap between the total scalp and medial frontal IC projections during the time of the ERN and NoGo N2, and clear MFN topographies. Although less of the total scalp data is accounted for during the time of the FRN, there is a clear peak in the GFA for the medial frontal ICs and the topographical projection is less positive for error compared to correct feedback. To further demonstrate that the classified medial frontal ICs account for traditional MFN effects, we examined the residual ICs (i.e., after removing medial frontal classified ICs), across tasks, and the corresponding topographies during the time of the NoGo N2, FRN, and ERN. As shown in Figure 3.3, the topographical maps during the timing of the NoGo N2, FRN, and ERN, do not reflect
activation of a recognizable MFN, suggesting that the MFN effects that are traditionally scored at the scalp are well accounted for by the medial frontal ICs that were classified using our response cueing task.

**Figure 3.3** Topographical maps of border change MFN IC back projections (left, black boxes) and residual data (right, red boxes) during the NoGo N2 (top left), FRN (bottom left), and ERN (right) from the Go/No-Go (top), Time Estimation, and Letter Flanker tasks. The waveforms show the global field amplitude of the difference between conditions for the entire scalp data (green), MFN ICs (black), and residual ICs (red). The shaded axis area highlighted the latency window of the traditional MFN effects and timing used to derive the topographical maps.
**Medial frontal IC theta power**

All time-frequency spectrograms and reliability tally plots are masked at the 99% confidence interval so that only significant z-scores are shown in colour. Grand average contrasts show that, for the border colour change medial frontal ICs, theta power is reliably modulated for stimulus-locked N2 and response-locked ERN effects across each of the four performance monitoring tasks (see Figures 3.4 and 3.5).
Figure 3.4 Summary of stimulus-locked N2 effects across tasks and subjects for the border colour change medial frontal ICs. The first column shows the ERPs (site FCz), the second column shows the bootstrapped spectral condition overlays, the third column shows the bootstrapped z-score differences in spectral power, and the fourth column shows the consistency of significant condition effects across single subjects. The time-frequency plots in columns three and four are masked at the 99% confidence interval to show in colour only those power values that significantly different between conditions. Vertical lines represent the boundaries for the N2/P3 complex. Horizontal lines represent the boundaries of the theta frequency band.
Figure 3.5 Summary of response-locked ERN effects across tasks and subjects for the border colour change medial frontal ICs. The first column shows the ERPs (site FCz), the second column shows the bootstrapped spectral condition overlays, the third column shows the bootstrapped $z$-score differences in spectral power, and the fourth column shows the consistency of significant condition effects across single subjects. The time-frequency plots in columns three and four are masked at the 99% confidence interval to show in colour only those power values that significantly different between conditions. Vertical lines represent the boundaries for the ERN/Pe complex. Horizontal lines represent the boundaries of the theta frequency band.

The average likelihood of finding a reliable effect for response-locked ERNs across individuals was 92%, with only 2 subjects exhibiting less than a 50% chance that medial frontal theta differentiates between correct and error trials (subjects 3 and 9,
shown below; see Figure 3.6). Similarly, there was a 73% likelihood of finding reliable stimulus-locked N2 effects across individuals, with only 3 subjects showing less than a 50% chance that medial frontal theta differentiates between conditions (subjects 3, 8, and 9, shown below; see Figure 3.7).
Figure 3.6 Tally plots indicate the reliability across time and frequency of finding a stimulus-locked N2 effect in each subject. The tally is aggregated based on $z$-scores that exceed the 99% confidence internal (i.e., $z$-score > 2.326) for N2 effects across the different performance monitoring tasks. Vertical lines represent the boundaries for the N2/P3 complex. Horizontal lines represent the boundaries of the theta frequency band.
Figure 3.7 Tally plots indicate the reliability across time and frequency of finding a response-locked ERN effect in each subject. The tally is aggregated based on z-scores that exceed the 99% confidence internal (i.e., $z$-score > 2.326) for ERN effects across the different performance monitoring tasks. Vertical lines represent the boundaries for the ERN/Pe complex. Horizontal lines represent the boundaries of the theta frequency band.
These data clearly show that the reliable effects of IC spectral power are consistent and well isolated across both time (200 - 500 ms for stimulus-locked N2/P3 complex, 100 - 300 ms from response-locked ERN/Pe complex) and the theta frequency range (approximately 3 to 7 Hz). The stimulus-locked N2 and response-locked ERN effects are elaborated on in the following sections, separated by performance monitoring task.

**Stimulus-locked N2 effects**

*Response cue task.* The summary figures for stimulus-locked N2 effects in the response cue task show that modulation of medial frontal theta is reliable for all categorical contrasts. Across subjects, the border colour change effects observed here replicate the findings reported in van Noordt et al. (2015a). Specifically, increases in theta power to border colour change trials are more reliable across subjects when the response cues signal a need for high cognitive control (i.e., CP [70%] and PP [63%]) as compared to cues signaling that upcoming trials are predictable and require a pre-potent response (i.e., PC [41%] and CC [52%]). The most reliable effect of increased theta found across subjects was for successful response inhibition to NoGo stimuli (82%).

*Go-NoGo task.* Similar to the response cue task, there was a robust effect of NoGo N2 theta modulation in 96% of subjects. These findings clearly show convergent validity between medial frontal activation during inhibition in traditional NoGo N2 tasks and our novel response cueing task.

*Time estimation task.* There was moderate reliability for increases in medial frontal theta corresponding to the FRN error and correct feedback. These findings suggest that robust increases in theta linked to the FRN in the time estimation task are less
consistent across subjects as compared to the N2 border colour change and NoGo N2 effects.

*Response locked ERN effects*

*Response cue task.* There was a reliable increases of theta power in 69% of subjects for medial frontal selected ICs following NoGo error compared to correct responses during the time of the ERN. The grand averages for this categorical contrast do not include data for subjects 1 or 15 due to an absence of response commission errors.

*Go-NoGo task.* Similar to the stimulus-locked N2 effects in the NoGo task, the response-locked ERN shows the most consistent reliability compared to the other tasks, with 92% of subjects showing increased theta power on NoGo trials. Increases in theta for medial frontal selected ICs were found for both standard error trials (i.e., error on a NoGo following a Go trial), as well as catch/repeat error trials (i.e., error on NoGo following a NoGo trial). The grand averages for this categorical contrast do not include data for subjects 7 or 15 due to an absence of response commission errors.

*Letter flanker task.* There was a reliable increase in theta power for medial frontal selected ICs following response-locked errors in the flanker task. Greater medial frontal theta following error compared to correct responses was reliable for both congruent and incongruent trials, with a greater number of subjects showing consistent effects for incongruent (89%) compared to congruent (69%) trials. The grand averages contrasting congruent trials do not include data for subjects 15 due to an absence of response commission errors.
Discussion

Much evidence points to the medial frontal cortex as an important neural substrate of cognitive control and the generator of several MFN ERP components that are elicited in performance monitoring tasks. We have shown here that these various MFNs can be accounted for by the same latent factor in single subjects' EEG and that theta oscillations are common to MFNs elicited during such performance monitoring tasks. Our analysis extends the traditional ERP approach by implementing advanced data processing and analytical techniques and, to our knowledge, is the first study to exploit the benefits of robust estimation using bootstrap re-sampling on the time-frequency data in order to assess the reliability of medial frontal theta effects between and within single subjects and across tasks.

Several studies have now documented similarity across MFNs in that some of them can be captured by the same latent components or models in the EEG signal (ERN and FRN: Gentsch et al., 2009; ERN and CRN: Hoffmann & Falkenstein, 2010; ERN and novelty N2: Wessel et al., 2012). In the current study we replicated more rigorously our method of functionally classifying medial frontal ICs using simple response cues that are unrelated to errors, response inhibition, or feedback, and show that these ICs account for the traditional NoGo N2, FRN, and ERN effects (van Noordt et al., 2015a). This is illustrated strongly in that, when we remove the medial frontal classified ICs, the remaining activation in the residual data does not correspond to a medial frontal source projection that characterizes MFNs. Our results also suggest that, although there is functional overlap across MFNs, there is some variation in the robustness of NoGo N2,
FRN, and ERN effects. In particular, feedback-related (FRN) modulation of theta was less consistent across subjects (i.e., fewer subjects showing greater theta to incorrect compared to correct feedback; 44%) compared to theta effects for the NoGo N2 (96% of subjects) and ERN (92% of subjects). Our data also show that the strength of bootstrapped theta effects is mirrored in their robustness across subjects, such that a greater number of subjects show significant effects when the z-score differences in theta between conditions are largest. Researchers have examined the oscillatory dynamics of these ERP components through the use of time-frequency decompositions and the perturbations in spectral power following task events known to elicit MFNs. A consistent finding is that MFNs share a common neural signature in theta rhythms, which have been linked to sources in the medial frontal cortex (Asada et al., 1999; Hoffmann et al., 2014; Ishii et al., 1999; Liu et al., 2014; Maurer et al., 2014). Across studies, medial frontal theta is found to increase during instances of response conflict, punishment/unexpected feedback, error commission, stimulus novelty, inhibitory control, rule violations, and response cueing (Cavanagh et al., 2010, 2012; Cavanagh & Shackman, 2015; Clayton, Yeung, & Cohen Kadosh, 2015; Cohen et al., 2008; Hajihosseini & Holroyd, 2013; Lavallee, Meemken, Herrmann, & Huster, 2014; Luu et al., 2004; Nigbur et al., 2011; Trujillo & Allen, 2007; van Noordt et al., 2015a). Direct intracranial recordings in humans converge with evidence from scalp recording potentials by showing that inter-regional theta encoding increases as a function of rule difficulty in a response control task (Voytek et al., 2015).

Increases in theta appear to be important for successful behavioural control (Cavanagh, Cohen, & Allen, 2009). In support of this, multiple studies have now
demonstrated that theta dynamics are related to adaptive response control, such as
overriding pre-potent stimulus-response associations (Cavanagh et al., 2013), optimal
behavioural adjustment following feedback (e.g., reinforcement learning; Cavanagh et al.,
2010; Luft et al., 2013), response adjustments between conflicting stimuli (e.g., stimulus-
response congruency; Ma et al., 2015), and post-error slowing (Cavanagh & Shackman,
2015). In a separate study, we found that increased medial frontal theta during response
preparation is a prerequisite for successful control over saccadic movements (van Noordt,
Desjardins, Gogo, Tekok-Kilic, & Segalowitz, unpublished). Consistent with this,
increasing theta synchrony via transcranial direct current stimulation (tDCS) stimulation
results in greater response control (Reinhart et al., 2015), suggesting that medial frontal
theta is critical for realizing the need for cognitive control in the face of dynamic
behavioural challenges.

Assessing the functional similarity across ERP components that are elicited by
different task events is an important line of research, which benefits greatly from the
methods used in the current study. These methods are not only useful for removal of
well-known artifacts in the EEG (Jung, Humphries, Lee, & Makeig, 1998), but they also
enhance the quality of hypothesis testing and interpretability of results. With respect to
medial frontal activation during performance monitoring tasks, ICA and bootstrapping of
time-frequency data is superior to traditional approaches restricted to the time domain of
scalp data and group-level parametric statistics. Scalp EEG is a mixed projection from
simultaneously active cortical sources, which limits the types of questions that can be
answered about brain function and the relation it may have to behaviour. For example,
deharical ERP approaches involve hypothesis testing and interpretation of brain signals
that contain a source projection of interest (e.g., medial frontal activity following
response commission; ERN) as well as activity from cortical sources that are potentially
unrelated or non-specific to the cognitive process that is being examined. By using
methods of blind source separation, including ICA, researchers are able to isolate the
activation of different cortical sources and perform hypothesis testing on the un-mixed
field projections. The utility of the ICA approach is continually garnering support among
researchers who have used this method to isolate source projections that include the P1,
N1, N170, N2, P3, ERN, and FRN ERP complexes (Debener, Makeig, Delorme, &
Engel, 2005; Desjardins & Segalowitz, 2013; Gentsch et al., 2009; Hoffmann &
Falkenstein, 2010; Jung et al., 2001; Makeig et al., 1999, 2002; Makeig & Onton, 2008;
Roger et al., 2010; Silvetti et al., 2014; van Noordt et al., 2015a; Wessel et al., 2012).
Similarly, using such methods in the current study show that it is possible to isolate and
functional classify a specific cortical process and examine whether a cortical source
projection behaves similarly to different task events.

**Summary**

In this study we replicated and extended a method of functionally classifying
medial frontal ICs in single subjects, using a task that includes stimulus cues indicating
the potential need for changes in response control. We found that these medial frontal
classified ICs describe several well-established stimulus-locked N2 and response-locked
ERN effects in multiple performance monitoring tasks. Importantly, bootstrap re-
sampling of spectral data for these MFN ERPs showed that ERN, NoGo N2, and FRN
effects across four different tasks are functionally similar in that they all show a common
signature of increased theta power in the components isolated in our response cueing
task. These effects were strongest for the NoGo N2 and ERN, with moderate robustness in FRN effects. Using the outcome of the single subject bootstrap testing, we demonstrate that the medial effects are quite robust across individuals and tasks, being highly consistent across both time and the theta frequency range. These results add an important piece to the literature on medial frontal theta and cognitive control by showing that, in single subjects, multiple MFN effects are well accounted for by latent factors in the EEG signal, which can be isolated using simple response cueing paradigms.
Supplementary Figure 3.1 Comparison of medial frontal IC functional classification from two independent samples using response cueing task. The top panel is adapted from van Noordt et al. (2015a) and includes 12 subjects. The bottom panel is adapted from the current study and includes 27 subjects. Waveforms represent the GFA of the difference between Go and Border Colour Change trials for the total scalp data (green), medial frontal classified ICs (black), and residual ICs (red). Source estimates are shown on the right for both sLORETA and dipole models.
References


Chapter 4

Cognitive control in the eye of the beholder: Theta and alpha modulation during response preparation in a cued saccade task.

Abstract

The oscillatory dynamics of medial frontal EEG theta and posterior alpha are implicated in the modulation of attention and cognitive control. We used a novel saccade cueing paradigm to examine whether theta and alpha distinguish successful response preparation separately from response execution. After classifying medial frontal and posterior alpha independent components, the EEG spectral power in these sources was calculated on pro- and anti-saccade trials prior to response probes. The results of bootstrap re-sampling show that, compared to easy pro-saccade trials, correct anti-saccades are characterized by an increase in medial frontal theta and suppression of posterior alpha during the response preparation period. Furthermore, an absence of increased medial frontal theta prior to anti-saccade probes occurred on error trials, that is, a failure to control pre-potent eye movements. For these error trials, a burst in medial frontal theta is instead observed following error feedback. Our findings show that enhanced medial frontal theta is linked not only to dynamic cognitive control that is reactive (such as, after error commission), but that it is also an important prerequisite for success when behavioural control is challenged.
Introduction

Purposeful control of attention is required when strategizing and directing behaviour towards achieving goals, especially when preparing to overcome habitual and prepotent responses. The medial frontal cortex has been well-established as an important neural substrate of performance and response monitoring, particularly in contexts that are challenging and involve the need for rapid shifts in stimulus-response contingencies. Converging evidence from animal and human studies using intracranial recordings (Cristofori et al., 2013; Isomura et al., 2003; Womelsdorf et al., 2010), magnetoencephalography (MEG; Ishii et al., 1999), electroencephalography (EEG; Luu, Tucker, & Makeig, 2004; Trujillo & Allen, 2007; van Noordt, Desjardins, & Segalowitz, 2015a), functional magnetic resonance imaging (fMRI; Meltzer, Negishi, Mayes, & Constable, 2007), and transcranial direct current and magnetic stimulation (TMS; Ott, Ullsperger, Jocham, Neumann, & Klein, 2011) shows that activation in frontal sources during performance monitoring is consistently linked to signals in the theta frequency range (~3 to 8 Hz). In addition to theta modulation, suppression of posterior alpha rhythms is also commonly observed when individuals are required to focus on task demands and be vigilant about their response selections (Chen, Feng, Zhao, Yin, & Wang, 2008; O’Connell et al., 2009; van Driel, Ridderinkhof, & Cohen, 2012). Together, the oscillatory dynamics of frontal theta and posterior alpha may be important markers of cognitive control, especially when preparing to override a pre-potent response tendency.

In the current study using a novel saccade-cueing task, we found that medial frontal theta and posterior alpha are modulated by response cues signaling the relative difficulty of impending eye saccades. In contrast to traditional performance-monitoring
paradigms that focus on evoked brain responses, we consider the role of theta and alpha in relation to the cognitive state that is induced while individuals prepare for a response probe. Importantly, we show that the failure to appropriately control a pre-potent eye movement characterized by a lack of medial frontal theta power prior to the response, that is, during the preparation stage. Our results expand our understanding of the role of the medial frontal cortex and its generated EEG theta beyond its traditional association with activity evoked by stimuli or by response outcomes to that of response preparation as a prerequisite for successful control over behaviour.

**Medial frontal cortex, cognitive control, and theta activity**

There is much evidence that EEG theta rhythms reflect the activation in medial frontal sources that is often observed in performance monitoring paradigms (Cavanagh & Shackman, 2015; Cavanagh et al., 2012; Nigbur et al., 2011). In particular, several medial frontal negativity ERP components, which oscillate in the theta frequency, have been linked to response errors, inhibition, and outcome evaluation, as well as to the processing of novel, surprising, or unexpected feedback (Cavanagh et al., 2012; Narayanan et al., 2013). These stimulus and behavioural events, such as the commission of errors (Cohen, 2011; Luu et al., 2004; Trujillo & Allen, 2007) and the responses to negative or unexpected feedback (Cohen et al., 2008; Hajhosseini & Holroyd, 2013), evoke increases in theta power. Akin to errors, which indicate the need to change response control, theta activity at medial frontal sites increases as a function of expectancy violation (Cavanagh et al., 2010) and in the presence of response conflicts (Cohen & Cavanagh, 2011) such as those introduced by NoGo or flanking stimuli (Nigbur et al., 2011). Furthermore, changes in medial frontal blood-oxygen-level-dependent (BOLD)
signals following response errors are associated with EEG theta band activity (Hoffmann et al., 2014). Although many studies have shown that medial frontal theta oscillations are important for understanding attention in the service of cognitive control (Clayton, Yeung, & Kadosh, 2015), this research is focused on EEG associated with activity that is evoked by specific behavioural responses or specific stimuli. Consequently, there has, to date, been little research focused on theta dynamics during periods of response preparation in humans. Such studies are important for determining whether the presence of medial theta is simply a co-requisite for performance monitoring or if, in fact, it is also a pre-requisite for staging successful cognitive control.

More direct evidence for theta modulation during response preparation is found in non-human studies showing that theta activity is increased during the preparatory/anticipatory stages of response selection or execution. For example, recording from neurons in the primate anterior cingulate cortex (ACC) shows that theta-band activity is linked to response selection and execution (Isomura et al., 2003), and that increases in theta occur in macaques during response preparation (Womelsdorf et al., 2010). Medial frontal theta activity also increases prior to self-initiated movements (Tsujimoto, Shimazu, & Isomura, 2006) and has been found to predict which stimulus-response mapping will be executed following the presentation of a visual target (Womelsdorf et al., 2010a). Similar findings have been reported in rats, such that behavioural choices are predicted by increases in ACC-prelimbic theta synchrony prior to response cue onset (Totah et al., 2013). Thus, recruiting executive control to resolve behavioural challenges is commonly linked to modulation of theta-band activity in medial frontal neurons in studies with non-human samples.
Attention and posterior alpha activity

Alpha frequencies represent a major component of human EEG and have been investigated in several experimental contexts. The literature on alpha activity is complex and includes evidence of a variety of changes in alpha as a function of task demands. For example, alpha oscillations have been found to increase as a function of working memory load during retention periods (Jensen, Gelfand, Kounios, & Lisman, 2002). Indeed, some researchers report alpha increases as a function of task difficulty, but these studies often focus on visual-spatial working memory tasks (Jensen et al., 2002; Klimesch, Sauseng, & Hanslmayr, 2007) as opposed to performance monitoring and speeded response tasks (e.g., Go/NoGo, Letter Flanker), which are the focus of the current study. In the context of these tasks, alpha activity reflects the “idling” of the cortex and is suppressed during bouts of increased attentional demand. Furthermore, alpha is highly synchronized in regions that together form the default mode network (Jann et al., 2009), which is engaged during resting states and when demands on stimulus processing are minimal. Alpha oscillations in the human EEG often show peak activity at parietal and occipital scalp sites (Adrian & Matthews, 1934; Hamm, Sabatinelli, & Clementz, 2012). As an index of cortical excitability (Romei, Rihs, Brodbeck, & Thut, 2008), power in the alpha spectrum at posterior sites is larger while individuals are at rest with their eyes closed compared to at rest with eyes open (Chen et al., 2008), showing an inverse relationship between alpha power and external attentional demands. Furthermore, alpha band activity has been found to reliably increase leading up to a missed target in a continuous expectancy task (O’Connell et al., 2009), suggesting that either low attentional control or vigilance to the task coincides with a state of heightened alpha power (van Driel et al., 2012).
Related to the goals of the current study, multiple researchers report reductions in alpha power in tandem with changes in theta activity when demands on attention and behavioural control are relatively high. Together, changes in alpha and theta during performance monitoring likely reflect the establishment of task-related activity (Belyusar et al., 2013) and network mechanisms that support sensory gating in service of cognitive control (Sadaghiani et al., 2012). For example, alpha phase locking and power in parietal and occipital regions are reduced prior to cue onset (Hamm, Dyckman, McDowell, & Clementz, 2012) and following behavioural responses on errors trials (van Driel et al., 2012). During these instances of failed behavioural control, inter-regional theta activity in the frontal cortex is enhanced (van Driel et al., 2012) and has been shown to correlate negatively with BOLD signals in the default mode network (Scheeringa et al., 2008). Similarly, using an anti-saccade task, Belyusar et al. (2013) found that alpha suppression to target letters was inversely related to theta activity. Taken together, these studies support the notion that volitional control of attention and moment-to-moment changes in response demands are characterized by suppression in posterior alpha oscillations and enhancement of theta-band activity in frontal regions.

The current study

By using a novel response cueing saccade task, we tested the hypothesis that frontal theta and posterior alpha are sensitive to the cognitive preparatory demands of the task. Unlike traditional approaches, our novel saccade task introduces a delay period between cues signaling whether the trial required a pro- or an anti-saccade to subsequent presentation of peripheral response probes. Thus, in addition to examining oscillatory dynamics as a reactive response to behavioural outcomes (e.g., following error
commission or feedback), we consider whether theta and alpha modulation are functional *prerequisites* to successful behavioural control when overcoming habitual responses.

**Methods**

**Participants**

Twelve healthy young adults volunteered to participate in the current study, all of whom were right handed and had normal or corrected-to-normal vision. EEG data for one subject were excluded due to excessive artifacts during recording. The remaining 11 participants consisted of 7 males and 4 females, with a mean age of 25 years ($SD = 2.87$ years). Participation was voluntary and involved no monetary incentives. The study received clearance from the Brock University Bioscience Research Ethics Board and all participants provided informed consent.

**Pro-/anti-saccade delay task**

We modified the traditional Go-NoGo paradigm to create a novel task in which participants were required to make frequent pro-saccades and infrequent anti-saccades to peripheral probes. For the duration of the task, three squares were always present on the screen, including a central square which provided information about the trial type (i.e., a cue for an upcoming pro-saccade or anti-saccade trial) and two peripheral borders (left and right) where the response probe could appear (see Figure 4.1). Trials were initiated by having participants focus their gaze on the central square for 200 ms, at which point a fixation cross was presented for 50 ms. The colour of the fixation cross was either white or black and signaled that the trial required either a pro-saccade (e.g., white fixation) toward or an anti-saccade (e.g., black fixation) away from the peripheral response probe. After a delay of 800 ms, a response probe flashed for 50 ms in one of the peripheral
squares. Thus, depending on the colour of the central cue, participants were required to respond either by looking at the square where the peripheral response probe appeared (pro-saccade), or at the square opposite to where the probe appeared (anti-saccade). A fixation of at least 30 ms at a peripheral square was required for responses to be logged. Immediately following a response, feedback, which consisted of a check mark for correct responses or an “X” for incorrect responses, was presented for 200 ms inside the peripheral square where the response was made. Participants were then required to return their gaze to the middle square in order to initiate the next trial.
Figure 4.1 Schematic illustration of task parameters. The left panel shows the temporal sequence for a single trial, beginning with fixation and ending with feedback. The right panel is an example the response context indicated by border color. This example represents all stimuli features used in the task. Response context and saccade cue were counterbalanced across subjects.

Features of this saccade task were modeled from a response cuing task that we developed and previously used to examine medial frontal activation (van Noordt et al., 2015a). Pro- and anti- saccade trials occurred within specific blocked contexts, which were indicated by the border colour of the middle square. There were two principal contexts: The “Certain” context indicated that the participant would only be presented with central cues signaling a pro-saccade response (e.g., all fixation crosses would be
white), while the “Possible” context included central cues signaling that trials could consist of both pro-saccade or anti-saccade responses. These two contexts were defined by the border color of the middle square, whereby a white or black border indicated the “Possible” context, and a blue or red border indicated the “Certain” context, or vice versa as per counterbalancing across participants. The colour of the middle context border changed, randomly with a range of three to seven trials, simultaneously with the onset of the central cue, and could change from a Certain to a Certain context (CC), Certain to Possible (CP), Possible to Certain (PC), and Possible to Possible (PP). As an example, for half the counterbalanced sessions, blue and red context border colours indicated the presence of only pro-saccade trials, whereas white and black context border colours indicated the presence of a combination of pro- and anti-saccade trials. These associations were counter-balanced across subjects, along with the colour of the central cues differentiating pro-saccade and anti-saccade trials. Participants were informed of all task parameters and the context details before beginning the task, and were free to strategize behaviour across trial contexts without the need to gradually learn the appropriate stimulus-response, fixation cue, and border context associations. See Figure 4.1 for a summary of trial details.

The task was performed in four blocks, each lasting approximately eight minutes, depending on participant response times. Each participant completed a total of 896 trials, which were broken down into the following trial types: 512 pro-saccade trials without border switches (320 during Certain contexts, 192 during Possible contexts), 256 pro-saccade context switch trials (64 × four types: CC, CP, PC, and PP), and 128 anti-saccade trials during Possible contexts. Peripheral probes appeared an equal number of times in
the left and right peripheral borders for each trial type (e.g., 64 left probe and 64 right probe anti-saccade trials, 32 left probe CC and 32 right probe CC trials). This sample is part of a larger on-going study and our specific interest was to examine the dynamics of theta and alpha power from medial frontal and posterior sources, respectively, during the delay period between the presentation of the saccade cue and the onset of the peripheral probe. Therefore, we focused on comparing only those pro- and anti-saccade trials that occurred during the “Possible” context given that each trial type is unpredictable until the saccade response cue is presented.

This study relied on the integration of the E-Prime (version 2.0, Psychology Software Tools, Inc.), Smart Eye Pro (version 5.8, Smart Eye AB), and Net Station (version 4.5.1, EGI, Inc.) software to present the saccade-cueing task, as well as record the spatio-temporal dynamics of saccades and EEG. All participants were secured in a chin rest that was placed at a fixed height to minimize neck tension, head movements, and changes in visual angle to the screen during the task.

**Electrophysiological recordings and data reduction**

EEG data were acquired using a 128-channel HydroCel Geodesic Sensor Net (HCGSN; EGI, Inc.), equipped with Ag/AgCl electrodes, and a 300 series amplifier. Signa Gel (Cortech Solutions, Inc.) was used as an electrolyte medium, and impedances were verified at 100 kOhms or lower prior to recording. Recordings were collected with a sampling rate of 500 Hz, 100 Hz low pass filter, 0.1 Hz high-pass, and referenced to site Cz.

Offline, EEG data were submitted to an automated pre-processing pipeline and then bootstrap testing using EEGLab (Delorme & Makeig, 2004). Custom in-house code
was created using MATLAB 2010b and executed in Octave 3.6.3 on the Shared Hierarchical Academic Research Computing Network (SHARCNet). The systematic automated processing stream follows closely the steps described in detail by Desjardins and Segalowitz (2013), as well as van Noordt et al. (2015a) and van Noordt, White, Wu, Mayes, and Crowley (2015b). Briefly, processing the EEG data involved the flagging of channels and in-task time based on channel-neighbour correlation distributions. The goal of this stage of the processing pipeline is to identify and remove artifacts in order to increase the quality of blind source separation using independent component analysis (ICA). There were, on average, 13 channels (SD = 5, ranging from 7 to 21) removed before performing the ICA (Bell & Sejnowski, 1995; Jung et al., 2001; Makeig et al., 2004). After this initial ICA, a similar flagging procedure that was applied to the channel data was carried out on the standard deviation of the IC time courses to identify and remove periods of activation during which at least 10% of the components were outside of their own 99% confidence interval. The second ICA was applied to the remaining continuous signal, low-pass filtered at 30 Hz.

**Classification of independent components**

Subsequent to fitting the field projection weight matrix of each IC (dipfit plug-in for EEGLab; Oostenveld, Fries, Maris, & Schoffelen, 2011), cortical classification of ICs was performed to remove from the EEG signal those components that were non-cortical (i.e., stationary noise signals, biological artifacts). ICs were removed on the basis of residual dipole variance of 15%, IC topographies, and their continuous signal. Specifically, manual examination of topographies and continuous signals was done to remove stable non-cortical ICs that describe biological (i.e., EMG, ECG, EOG) or single
channel artifacts. After purging flagged times and ICs, the data were filtered 1 to 30 Hz and re-referenced to the average of 19 interpolated sites. Across subjects an average of 12 cortical ICs ($SD = 4.42$, ranging from 6 to 21) were retained from this classification process.

Prior to hypothesis testing, the cortically classified ICs were examined to identify in each subject ICs reflecting medial frontal projections and posterior sources generating alpha-band activity. ICs were classified independent from the saccade cues that were used for hypothesis testing. Specifically, ICs with a medial frontal projection were retained if a single dipole fit had a residual variance of less than 10% and the absolute value of the peak projection was maximal at, or adjacent to, Cz and FCz midline sites. A single medial central/frontal IC was retained for 7 subjects, whereas four subjects had 2 medial frontal projecting ICs that met classification criteria. In these four subjects, the mean of the combined projection was used for hypothesis testing. See Figure 4.2 for a summary of the selected medial frontal ICs and their residual variance.
Given that border colour change trials in our task signal the potential need for increased vigilance, we focused on the Certain-Certain (CC) border changes to assess alpha suppression because they make minimal demands on response control compared to other border change trials and are independent of the events used for hypothesis testing. Classifying posterior ICs that generate alpha rhythms was therefore done by examining event-related spectrograms for CC trials and the continuous time course activity. An IC was classified as a generator of posterior alpha if the source projection (i) produced peak

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**Figure 4.2** Topographical maps of medial frontal ICs that were retained for hypothesis testing. The top panel shows the grand average medial frontal IC projection and dipole fit. Bottom panel shows the single subject medial frontal IC projections. Percentages reflect the residual variance of a single dipole for each medial frontal IC that was retained. The polarity of the topographies are arbitrary.
activation focused over posterior/occipital regions, (ii) showed a reduction in event-related alpha power following CC border changes, and (iii) had explicit periodic oscillatory peak in ongoing alpha. These criteria allowed us to retain between 3 and 5 posterior ICs per subject, which were clustered to represent posterior alpha.

**Time-frequency decomposition of classified independent components**

Our analyses focused on comparing activity in medial frontal and posterior alpha ICs during the delay period between saccade cues and the peripheral response probes for pro- and anti-saccade trials. Epochs were time-locked to the onset of saccade cues, 2000 ms preceding and 2850 ms succeeding each cue. A baseline of –200 to 0 ms was used for all segments. There was an average of 168 (SD = 33) and 114 (SD = 21) artifact free trials for pro- and anti-saccade cues, respectively. The EEGLab function “newtimef” was used to decompose the single trial EEG data into time-frequency spectrograms. Event-related activity was convolved into spectral power using Morlet wavelets, with cycles increasing from 1 at 1 Hz to 10.5 at 20 Hz. This time-frequency transformation provided us with event-related spectral perturbations (ERSPs) for medial frontal and posterior alpha IC clusters.

**Statistical analyses and robust estimation**

Robust estimation techniques are ideal for dealing with small sample sizes and avoiding issues that arise when violating assumptions of traditional parametric tests (Wilcox, 2005). Given that robust parameter estimates provide greater control over measures of location, alpha levels, and unrepresentative confidence intervals (Wilcox & Keselman, 2003; Wilcox, 2005), their utility in EEG research is evident in quantifying effects of event-related activity across all time points (Desjardins & Segalowitz, 2013;
Rousselet, Husk, Bennett, & Sekuler, 2008; Rousselet & Pernet, 2011; van Noordt et al., 2015a). In this study we used trimmed means and bootstrap re-sampling to assess differences in brain activity to task events. ERSP contrasts used a 20% trimmed mean and 1000 bootstrap samples to assess categorical differences, at each time point. Thus, we selected with replacement n trials from each condition, trimmed 20% of the trials (i.e., top 20 and bottom 20 ranked values), and calculated the difference between conditions at each time point. Iterating this process 1000 times creates a distribution of ERSPs and allows the calculation of confidence intervals around the differences. Activation differences between conditions were assessed by comparing surrogate distribution values against the 99% confidence interval (i.e., standard z-score of +/- 2.326). There was no trial cap for ERSP analyses, and therefore all available trials were used to create surrogate distributions.

Behavioural analyses involving mean accuracy and reaction time values were performed using a robust ANOVA procedure that involves bootstrap re-sampling to assess differences in categorical contrasts. Through re-sampling of the raw data a distribution of difference scores was obtained, and the mean of these differences was then calculated after trimming 20% of the ranked values from each tail. This process of re-sampling, trimming, and mean calculation was repeated 1000 times. Follow-up pair-wise comparisons also included bootstrap re-sampling to determine whether a given categorical contrast is significantly different from the null hypothesis.
Results

Behavioural

Accuracy

Accuracy for pro-saccade trials approached ceiling levels ($M = .96$, $SD = .06$).

Although accuracy for anti-saccade trials was, as expected, marginally worse and more variable ($M = .85$, $SD = .15$) compared to pro-saccade trials ($p < .05$, 95% CI [-0.04, -0.16]), performance across subjects was quite high. With the exception of subject 6 who performed near chance levels for anti-saccade trials, all participants achieved an accuracy of 80% or higher.

Reaction times

Reaction times were calculated as the latency difference between the onset of a peripheral response probe and the onset of response feedback. From this difference, a constant of 30 ms was subtracted to account for the fixation time required for the response to be registered and feedback to be presented. Average saccade response times varied as a function of trial difficulty and accuracy (see Figure 4.3).
Figure 4.3 Bar graph showing individuals' mean saccade response time for pro-saccade error (black), pro-saccade correct (blue), anti-saccade error (green), and anti-saccade correct (red) trials. Error bars reflect single subjects' standard error of the mean.

Pro-saccade errors trials had the shortest latency and were not included in statistical analysis of response times because these were highly infrequent across subjects (M = 7.9) and suspiciously fast (M = 146.89 ms), indicating that these responses reflect impulsive, unplanned, and non-systematic eye movements. Performing a one-way repeated measures robust ANOVA revealed a significant difference across response times for pro-saccade correct, anti-saccade correct, and anti-saccade error (p < .001).

Follow-up pair-wise comparisons indicated that pro-saccade correct (M = 309.26) responses were significantly faster than anti-saccade correct (M = 346.13) responses (p < .01, 95% CI [-17.60, -56.09]), but were not reliably different from anti-saccade (M = 304.72) error responses (p > .05, 95% CI [43.55, -38.84]). Finally, anti-saccade error responses were significantly faster than anti-saccade correct response (p < .01, 95% CI [79.37, 7.79]). This pattern of responses aligns with the difficulty of the various eye-movements, such that anti-saccade correct trials, which are the most difficult and require
successful inhibition of a pre-potent behaviour, had the longest latency. In addition, anti-saccade error trials and pro-saccade correct trials had similar latencies for responses to peripheral probes. This similarity in response times is to be expected given that anti-saccade errors are trials in which subjects made a pro-saccade to the peripheral probe, and should therefore be similar to pro-saccade correct trials.

**Electrophysiological**

*Theta and alpha power*

*Anti-saccade error and pro-saccade correct.* Theta power in medial frontal ICs during the timing of feedback was greater for anti-saccade error compared to pro-saccade correct trials. As illustrated in Figure 4.4, processing error feedback is characterized by an increase in theta power for medial frontal sources, as well as a decrease in alpha power for posterior sources. The 3-D plots at the top of Figure 4.4 show spectral power, across time and frequency, in the medial frontal (left) and posterior alpha (right) IC clusters for pro-saccade correct and anti-saccade error trials. The 2-D plot illustrates the $z$-score difference in spectral power between pro- and anti-saccade correct trials across time and frequency. The plot is masked to only show in color those values that exceed the 99% confidence intervals. Data points in green indicate greater (i.e., $z > 2.326$) medial frontal IC activity and grey data points highlight greater suppression (i.e., $z < 2.326$) in posterior alpha ICs for anti-saccade error compared to pro-saccade correct trials. Thus, the presentation of error feedback on anti-saccade trials is associated with increases in medial frontal theta and suppression of posterior alpha.
Figure 4.4 The top panel of 3-D plots shows time-frequency overlays for spectral power in medial frontal (left) and posterior alpha (right) IC clusters, contrasting pro-saccade correct and anti-saccade error trials. There is a reliable increase in medial frontal theta (green) and a decrease in posterior alpha (dark grey) following error feedback on anti-saccade trials. The bottom panel of 3-D plots shows time-frequency overlays for spectral power in medial frontal (left) and posterior alpha (right) IC clusters, contrasting pro-saccade and anti-saccade correct trials. During the delay period there is a reliable increase in medial frontal theta (red) and a decrease in posterior alpha (blue) on anti-saccade correct trials. The central 2-D plot shows the z-score condition differences
in medial frontal and posterior alpha clusters, masked at the 99% confidence interval (i.e., $z \pm 2.326$). Green data points indicate greater activation in medial frontal ICs on anti-saccade error trials, whereas dark grey data points indicate a decrease in power for posterior alpha ICs. Red data points indicate greater activation in medial frontal ICs on anti-saccade correct trials, whereas blue data points indicate a decrease in posterior alpha ICs. Coloured vertical lines indicate the range (+/- 1 SD) of mean saccade response times for pro-saccade correct (blue), anti-saccade correct (red), and anti-saccade error trials (green), which also signifies the approximate timing for feedback onset.

Note: PS C = Pro-Saccade Correct, AS E = Anti-Saccade Error, AS C = Anti-Saccade Error.

**Anti-saccade correct and pro-saccade correct.** Central to our hypothesis was whether there are differences in activation during the delay period between saccade cue and response probe for pro-saccade and anti-saccade correct trials. The expectation is that, compared to pro-saccades, correct anti-saccades are relatively more difficult to prepare and execute given the need to override a pre-potent response and that the induced cognitive state will be reflected in theta rhythms. We found that spectral power was modulated on correct trials as a function of saccade type. The 3-D plots at the bottom of Figure 4.4 show spectral power, across time and frequency, in the medial frontal (left) and posterior alpha (right) IC clusters for pro- and anti-saccade correct trials. Specifically, compared to pro-saccade trials, we observed increases in theta power in medial frontal ICs and suppression of alpha power for posterior ICs during the delay period between an anti-saccade cue and peripheral response probe. The 2-D plot illustrates the $z$-score difference in spectral power between pro- and anti-saccade correct trials across time and frequency. Data points in red indicate greater (i.e., $z > 2.326$) medial frontal IC activity and blue data points indicate suppression (i.e., $z < -2.326$) in posterior alpha ICs for anti-saccade correct trials. It is clear that reliable effects start to emerge after the presentation of the saccade cue and span until the presentation of a peripheral probe. These results show that, compared to pro-saccade cues, there is a
simultaneous increase in medial frontal theta and suppression of posterior alpha when individuals successfully preparing an anti-saccade to the impending response probe.

Anti-saccade correct and anti-saccade error. To validate the role of medial frontal theta for successful response control it is necessary to show that enhanced theta occurs during response preparation for anti-saccade correct compared to error trials. In contrast to the medial frontal theta effects observed while individuals correctly prepare for an anti-saccade response, there was no reliable increase in theta during the delay period for anti-saccade trials on which an error was committed. Instead, on error trials a burst of theta occurs around the time of feedback presentation (see Figure 4.5).
Figure 4.5 The 3-D plots shows time-frequency overlays for spectral power in medial frontal (top left) and posterior alpha (top right) IC clusters, contrasting anti-saccade correct and anti-saccade error trials. During the delay period there is a reliable increase in medial frontal theta (light grey) on anti-saccade correct compared to anti-saccade error trials. In contrast, there is a reliable increase in medial frontal theta (green) on anti-saccade error compared to anti-saccade correct trials following the presentation of response feedback. In posterior alpha ICs there is greater suppression of power on anti-saccade error compared to anti-saccade correct trials. The central 2-D plot shows the z-score condition differences in medial frontal and posterior alpha ICs, masked at the 99% confidence interval (i.e., $z \pm 2.326$). Data points in light grey indicate greater medial frontal IC activity on correct anti-saccade trials, whereas data points in green indicate greater medial frontal IC activity on anti-saccade error trials. For posterior alpha ICs, data points in dark grey indicate suppression of power for anti-saccade error trials. Coloured vertical lines indicate the range (+/- 1 SD) of mean saccade response times for pro-saccade correct (blue), pro-saccade, anti-saccade correct (red), and anti-saccade error (green) trials, which also signifies the approximate timing for feedback onset.

Note: AS E = Anti-Saccade Error, AS C = Anti-Saccade Correct
We verified further the effects reported above by extracting the peak activation for medial frontal and posterior alpha ICs in the theta and alpha frequency bands, respectively, and assessing the differences between conditions against the 99% confidence interval. As shown in Figure 4.6, there is a reliable increase in medial frontal theta power during the delay period on anti-saccade compared to pro-saccade correct trials, as well as anti-saccade correct compared to anti-saccade error trials. In addition, there is a reliable increase in medial frontal theta following anti-saccade error compared to anti- and pro-saccade correct feedback. Posterior alpha effects are less specific to task events, such that suppression is observed during response preparation on anti-saccade correct compared to pro-saccade correct trials, as well as on anti-saccade error compared to pro-saccade correct trials. Following performance feedback, alpha power is reduced on anti-saccade error compared to anti- and pro-saccade correct trials.
The waveforms show the peak spectral power, across trials, in theta and alpha bands for medial frontal theta (top plot) and posterior alpha (bottom plot) IC clusters. The transparent overlays below the waveforms show the upper and lower confidence intervals for each categorical contrast. For medial frontal ICs, there is a significant increase in theta during the delay period on anti-saccade correct trials compared to pro-saccade correct (red confidence intervals) and anti-saccade error trials (grey confidence intervals). There is also a significant increase in theta following response feedback on anti-saccade error trials compared to pro-saccade correct (green confidence intervals) and anti-saccade correct trials (grey confidence intervals). For posterior alpha ICs, there is a significant reduction in alpha power during the delay period for anti-saccade correct (red confidence intervals) and anti-saccade error (grey confidence intervals) compared to pro-saccade correct trials. Following response feedback there is a significant reduction in alpha power for anti-saccade error compared to pro-saccade correct (green confidence intervals) and anti-saccade correct (grey confidence intervals) trials. Coloured vertical lines indicate the range (+/- 1 SD) of mean saccade response times for pro-saccade (blue), anti-saccade correct (red), and anti-saccade error (green) trials, which also signifies the approximate timing for feedback onset.

Note: PS C = Pro-Saccade Correct, AS C = Anti-Saccade Error, AS E = Anti-Saccade Error
Discussion

Theta rhythms in the medial frontal cortex, and/or at medial frontal scalp sites, are a common signature of performance monitoring and cognitive control. It is well established that the medial frontal cortex is engaged when events demand a change in task set or response control, such as error commission, inhibitory control, feedback processing, stimulus-response conflicts, as well as events that are novel or unexpected (Forster & Brown, 2011; Jessup, Busemeyer, & Brown, 2010; Oliveira, McDonald, & Goodman, 2007; van Noordt et al., 2015a; Wessel & Ullsperger, 2011). In contrast to the evidence for event-related activations, less is known about the oscillatory dynamics associated with response preparation in humans. We used a novel saccade cueing task to isolate latent factors in the EEG and show that, compared to executing an automatic response, appropriately preparing to inhibit a pre-potent saccade is characterized by an increase in theta power in medial frontal sources and a decrease in alpha power in posterior sources. In addition, there is a lack of medial frontal theta during response preparation is characteristic of error commission trials, suggesting that this is a marker for the failure to establish adequate control over responses. In contrast, during these error trials, enhancement of medial frontal theta occurs during the presentation of error feedback. Thus, an increase in medial frontal theta during the anticipation of response probes appears to underlie successful cognitive control over pre-potent saccades.

Much evidence for medial frontal theta in the service of cognitive control is found across several post-response paradigms and multiple functional measures. Committing errors, inhibiting pre-potent responses, and facing response conflicts or unexpected events are all sufficient to transiently increase theta over the medial frontal cortex.
(Cohen, 2011; Luu et al., 2004; Trujillo & Allen, 2007; van Noordt et al., 2015a). For example, Nigbur et al. (2011) found that theta bursts consistently occur when cognitive demands are high, including response inhibition to NoGo stimuli, incongruent trials on a flanker task, and incompatible trials on a Simon task. Similarly, Cavanagh et al. (2012) found a common theta signature in the EEG for stimulus- and response-locked effects of novelty, conflict, and error processing. We have also shown previously, using a task similar to our current saccade paradigm, that there are increases in medial frontal theta in response to cues that signal a need for potential changes in response demands. This occurs even when these cues are not tied to response conflict, error commission, behavioural inhibition, reinforcement learning, or to the processing of feedback (van Noordt et al., 2015a). Thus, parsimoniously, one can describe the dynamics of theta oscillations over the medial frontal cortex as instances in which individuals realize a need for changes in attention allocation and cognitive control (Cavanagh & Frank, 2014; Holroyd & Yeung, 2012). In addition to previous studies, our results suggest that increases in medial frontal theta can be induced simply by the need to brace oneself for a potentially effortful response.

Our findings also show that the direct evidence from the animal work showing that theta-band activity of medial frontal neurons increases during response preparation (Isomura et al., 2003; Tsujimoto et al., 2006, 2010; Womelsdorf et al., 2010) can be confirmed in humans and is linked to response outcomes (Totah et al., 2013; Womelsdorf et al., 2010). In our task, successful control over reflexive saccade movements was underscored by theta enhancement while individuals prepared their response to an impending peripheral stimulus. Thus, we found, in humans, that a lack of theta
enhancement while preparing an anti-saccade resulted in a failure to direct eye movements away from a peripheral probe.

It has been proposed that medial frontal theta reflects a mechanism through which neuronal assemblies and networks integrate information from memory, bias sensory gating toward relevant stimuli or stimulus features, and modify task-sets in the face of dynamic environmental contingencies (Buzsáki & Draguhn, 2004; Klimesch, 1999). This theoretical framework can also accommodate the evidence for alpha suppression or asynchrony during bouts of high cognitive load and when task events or responses require for a change in attentional control (Sadaghiani et al., 2012). From this perspective, the transient increases and decreases in medial frontal theta and posterior alpha, respectively, could reflect the activation of networks involved in preparing and modifying response repertoires. For example, Cavanagh, Cohen, and Allen (2009) show that errors are associated with an increase in theta at medial frontal sites, whereas trials preceding error commission are characterized by reductions in theta power. These data are consistent with our results, showing an increase in theta power when there is a demand for attention and response modulation, and less theta during failed response control, likely due to attentional lapses. Given that posterior alpha is a reflection of cortical excitability and activation of the default mode network (Klimesch et al., 2007; Romei et al., 2008), which is deactivation of cortical networks associated with attention to external demands (Knyazev, Slobodskoj-Plusnin, Bocharov, & Pylkova, 2011), reductions in alpha ought to be observed when individuals must abort automatic and habitual response tendencies. Some have reported that alpha relates inversely to theta power (Belyusar et al., 2013), and others have shown that changing behaviour following
attentional lapses, as indicated by response errors, is associated with suppression of posterior alpha and increases in frontal theta activity (van Driel et al., 2012).

Our novel saccade cueing task offers several avenues for future research with clear testable hypotheses. As an example, to further uncover the network dynamics that support cognitive control, researchers could focus on temporal features of the functional relationships between cortical sources. In this approach, the application of methods such as Granger Causality could prove useful for assessing temporal precedence and whether medial frontal theta predicts subsequent suppression of alpha activity in posterior regions. Given the well known role of the frontal eye fields (FEFs) in preparing, executing, and modifying eye movements (Curtis, Rao, & D’Esposito, 2004; Offen, Gardner, & Heeger, 2010), it would be useful to isolate their field projections to better understand the underlying cortical networks supporting the control of eye movements. For example, activation in the FEFs varies depending on whether saccades are correct or incorrect, with FEF responses occurring prior to visual cortex activity on error trials (Herdman & Ryan, 2007), suggesting a network level communication between frontal and posterior sensory regions in support of orienting attention toward task relevant information (Medendorp, Buchholz, Van Der Werf, & Leoné, 2011). Others have suggested that the FEFs are involved in the top-down control over visual processing and allocation of visuospatial attention (Capotosto, Babiloni, Romani, & Corbetta, 2009; Hamm et al., 2012; Mazer, 2011). Together, these perspectives are in line with a framework in which suppression of posterior alpha during saccade tasks reflects sensory enhancement of task-relevant stimuli (Buchholz, Jensen, & Medendorp, 2014).
Summary

In this study we employed a novel saccade cueing paradigm and show that successful control of overt attentional deployment is characterized by increases in medial frontal theta and suppression of posterior alpha during response preparation. In addition, failure to appropriately prepare an anti-saccade is predicted by a temporal displacement of medial frontal theta. On error trials, instead of occurring during the response preparation period, a burst of medial frontal theta occurs following feedback. Although well established in the animal literature, we add to the evidence in humans for the role for "proactive" medial frontal theta during response preparation by showing that medial frontal theta may be an important prerequisite for successful response control.
References


Chapter 5

General Discussion

The role of the medial frontal cortex in controlled attention was examined in this dissertation by using novel response cueing tasks, advanced signal processing procedures, and robust estimation techniques for hypothesis testing. The goal was to test the idea that medial frontal cortex activation during performance monitoring can be described from a domain-general perspective, with an emphasis on the need for controlled attention, as opposed to isolated and specific interpretations based on the specific paradigm used (e.g., error processing, response conflict, inhibitory control, or reinforcement learning).

For study 1 we developed a novel response cueing task and successfully isolated, in each subject, medial frontal projecting ICs that were sensitive to border-change stimulus cues signaling the need for potential changes in response demands. These response cues also reliably affected task behaviour, such that individuals shifted to a slower response strategy when there was the possibility of facing a NoGo trial. This shift in response strategy predicted individual differences in inhibitory control on NoGo trials. Important to our hypotheses, the ERN and NoGo N2 were well explained by the functionally classified medial frontal ICs that differentiated Go from border-change trials. We also found that theta power in medial frontal ICs increased when individuals were alerted to potential changes in response demands, varying as a function of the cued demands; increases in theta were reliably greater for cues indicating the need for dynamic response control (i.e., "Possible" context; PP and CP cues) as opposed to cues signaling that responses would be predictable and habitual (i.e., "Certain" context; CC and PC cues). The fact that classified medial frontal activity was systematically related to cued
response demands, which were not tied to error commission, competing responses or response conflict, inhibition, reinforcement learning, or the evaluation of exogenous feedback, supports our model in which medial frontal cortex responses reflect the domain-general process of controlled attention modulation.

In study 2, with a larger sample than study 1, we successfully replicated our method of functionally classifying medial frontal ICs using a shortened version of our response cueing task. We also replicated the finding that increases in medial frontal theta to response cues were more reliable across subjects for those cues indicating the need for dynamic response control (i.e., "Possible" context; PP and CP cues) compared to cues signaling that pre-potent ballistic responding was sufficient for successful performance (i.e., "Certain" context; CC and PC cues). By including several other well-known performance monitoring paradigms, we provided further support for our model by showing that theta modulation in the classified ICs is consistent across multiple task events that describe traditional ERN, NoGo N2, and FRN effects. To our knowledge, this is the first study to provide such an in-depth analysis of the reliability of medial frontal theta effects between and within subjects across multiple paradigms.

The final study was designed to expand the predictions of our domain-general model of medial frontal function. To this end, we created a modified version of our original response cueing task to test whether medial frontal theta power is modulated during the preparation of controlled eye movements, as opposed to traditional effects focused on activity evoked by stimulus or response outcomes. This unique task allowed us to separate activity during response preparation/anticipation from activity related to overt responding. Our results support our model by showing that, compared to habitual
pro-saccades, preparing an anti-saccade response is characterized by an increase in medial frontal theta and suppression of posterior alpha power prior to responding. In addition, we found that failure to appropriately prepare and execute anti-saccade responses is linked to an absence of enhanced medial frontal delta/theta during response preparation, but that a burst of medial frontal slow-wave activity occurs following error feedback (rather than prior to response probing). These results show that enhanced slow-wave oscillations in the delta/theta range are linked not only to dynamic cognitive control that is reactive (e.g., error commission), but that these power changes are also a prerequisite to response preparation for success when behavioural control is challenged. These findings are consistent with a large body of literature focused on oscillatory dynamics and cognitive control, and further support our model that medial frontal activity during performance monitoring reflects a domain-general process of controlled attention.

**Domain-general role for medial frontal function**

During the past few decades several elegant models have been proposed to explain the neural correlates of performance monitoring and the functional significance of medial frontal activation in cognitive control. These models have tended to focus on specific MFNs and are interpreted within the context and paradigm being used to elicit the ERPs. Together, these models offer explanations for the MFN in terms of neural correlates of error detection (Gehring et al., 1993; Miltner et al., 1997; Miltner, 2003), conflict monitoring and response suppression (Botvinick et al., 1999; Nieuwenhuis et al., 2003; van Veen & Carter, 2002), processing exogenous performance feedback (Gehring & Willoughby, 2002), associative/reinforcement learning (Holroyd & Coles, 2008; Holroyd & Yeung, 2012; Holroyd & Coles, 2002; Nieuwenhuis, Holroyd, Mol, & Coles,
outcome expectancy deviation (Oliveira et al., 2007), and predicting the likelihood and timing of action outcomes on the basis of the ERN, NoGo N2, and FRN (Alexander & Brown, 2011). More recently, researchers have started to realize that the functional significance of multiple MFNs can be parsimoniously described from a domain-general perspective, such that the medial frontal cortex is activated to events that signal a need for optimization of attentional and response control.

One such domain-general model has been proposed by Cavanagh and colleagues (see Cavanagh & Shackman, 2015). These researchers provide meta-analytic evidence to support their adaptive control hypothesis, which suggests that a common signature of medial frontal theta describes MFNs that are associated with multiple stimulus or behavioural outcomes, and that these neural responses reflect the common need for cognitive control over goal-directed behaviour. Moreover, their hypothesis is an attempt to integrate the findings which show that anxiety and negative affect martial similar neural processes that are described by theories of cognitive control. Our model and the results of the studies presented here, although not focused on the integration of anxiety and control processes, are in line with a domain-general perspectives arguing that medial frontal theta is enhanced when individuals realize the need for cognitive control (e.g., Cavanagh et al., 2012; Narayanan et al., 2013).

**Theta and the coordination of neuronal communication to support behaviour**

Theta oscillations are not only a neural correlate of cognitive control, but have also been proposed as a neurophysiological mechanism that supports the coordination of local and large-scale network communication in the brain (Buzsáki, 2006). The notion that changes in theta power and phase synchrony reflect the temporal organization of
neuronal assemblies in different brain regions is supported by evidence from intracranial recording, performance monitoring, and working memory studies (Cavanagh & Frank, 2014; Cohen & Van Gaal, 2013; Jacobs, Hwang, Curran, & Kahana, 2006; Narayanan et al., 2013; Padrão, Rodriguez-Herreros, Pérez Zapata, & Rodriguez-Fornells, 2015; Rutishauser, Ross, Mamelak, & Schuman, 2010; Voytek et al., 2015; Womelsdorf et al., 2010). For example, theta activity of ACC neurons in macaques not only predicts the implementation of task rules, but also the behavioural adjustments following failures in response control (Womelsdorf et al., 2010). In humans, proactive and reactive behavioural control has been linked to functional connectivity of theta in multiple frontoparietal networks (Cooper et al., 2015).

Others have demonstrated that medial frontal theta during response/error monitoring serves as a neural hub that interacts with the oscillatory dynamics in posterior brain networks to support adaptive behavioural control (Cohen & Van Gaal, 2013). Similarly, intracranial recordings in human epilepsy patients performing a Stroop task show that conflict detection and behavioural adaptation are characterized by dynamic, and directionally specific, interactions of oscillatory interactions between dorsomedial and dorsolateral prefrontal cortex. Specifically, conflict detection engages dorsomedial prefrontal theta power which, in turn, predicts subsequent entrainment of dorsolateral prefrontal theta. Conversely, resolving behavioural conflict showed the reverse pattern of coupling, such that post-response dorsolateral gamma predicted subsequent increases in dorsomedial theta power (Oehrn et al., 2014). Also, using intracranial recordings in humans, Voytek et al. (2015) found that frontal theta is enhanced, along with local gamma activity, when responding to task rules that become progressively abstract.
Moreover, these increases in oscillatory phase dynamics predicted response times across single trials. Taken together, multiple lines of evidence suggest that frontal theta oscillatory dynamics reflect a neurophysiological mechanism for coordinating the canonical processes of cognitive control.

Although not the direct focus of this thesis, a noteworthy line of research demonstrates that theta oscillations are a neural correlate of cognitive operations that relate to working memory. Several researchers have found that medial frontal theta, localized to the ACC, increases as a function of memory load (Maurer et al., 2014) and predicts successful working memory manipulation (Itthipuripat, Wessel, & Aron, 2013; Rutishauser et al., 2010). More direct evidence comes from a study by Rutishauser et al. (2010) in which the authors collected intracranial recordings in humans while they performed a working memory task. Their results indicate that coordinated temporal theta spiking of hippocampal neurons predicted successful memory formation, such that coherence of theta spiking was 50% higher on trials for which target information was subsequently remembered compared to when it was forgotten. These results are intriguing for future research into the theta dynamics that characterize cognitive control, given that the hippocampal formation is a potent generator of theta rhythms (Gray & McNaughton, 2000), with some studies indicating that during certain behavioural states, such as exploration, hippocampal and frontal theta show transient coherence in their signal properties (Young & McNaughton, 2009). The events that signal the need for changes in attention in the service of adaptive behaviour could therefore reflect processes of memory formation and updating, such that current stimuli or responses in the task are compared to the mental representation of task goals (e.g., seeing a response cue that
signals upcoming trials are less predictable or require dynamic adjustments to response control, as is the case in our response cueing paradigms).

Considering our domain-general model, other fruitful lines of research could include examining theta across the lifespan and in clinical populations to clarify further the role of medial frontal theta in cognitive control. Assuming that theta dynamics are meaningful correlates of cognitive control, examining changes in theta could shed light on the behavioural manifestations that characterize variability in self-regulation across development and in special populations. Some recent research suggests that, indeed, theta dynamics differentiate aspects of cognition and behaviour in both developmental and clinical contexts. For example, Lithfous et al. (2015) found that enhancement of frontal theta during encoding is correlated with successful formation of cognitive maps required for spatial memory in young adults, whereas older adults showed poorer spatial memory and lower levels of theta. Similarly, Begus, Southgate, and Gliga (2015) studied infants while they performed an object exploration task and found that frontal theta predicted subsequent object recognition in a preferential-look test. Compared to normally developing controls, lower levels of frontal theta have also been linked to poorer performance in cognitive flexibility in children with autism (Yeung et al., 2015) and attentional lapses in children with developmental coordination disorder (Wang et al., 2015). Thus, profiles of frontal theta could help clarify the cognitive deficits that are typically observed in normal aging and in clinical populations that have limited self-regulation and behavioural control.
The application and utility of robust estimation techniques

The ultimate goal for most psychological research is to capture meaningful information that is pertinent to individuals in order to understand some aspect of their behaviour. In the field of cognitive and affective neuroscience, a richer understanding of the neural correlates of behaviour is currently limited by conventional ERP processing techniques, as well as the use of traditional statistical approaches to testing differences in ERPs averaged across groups. It is clear that these statistical and signal processing methods can impact directly upon the building, testing, revising, and application of theoretical models. Robust estimation techniques can address more efficiently such issues due to (1) their relative insensitivity to violations of statistical assumptions, and (2) their ability to provide a far more detailed picture of single trial intra-individual variability in ERPs.

As described above, several researchers have applied techniques of robust estimation in order to better understand brain-behaviour associations, resolve inconsistent observations, and clarify competing theoretical perspectives. However, the advantages of these techniques have only begun to be exploited in the cognitive neurosciences. In fact, it has been over 10 years since researchers first showed that robust estimation is a better way to deal with averaged ERPs from a small number of trials that are not likely normally distributed (see Leonowicz, Karvanen, & Shishkin, 2005). Nonetheless, “business as usual” in ERP research does not currently include a general awareness of these tools, knowledge of their application, or a willingness to see them implemented. I would like to stress that robust estimation can be used to capitalize on other aspects of
electrocortical signals, or to investigate research questions that may otherwise be untenable with traditional methods.

To reiterate a previous point, the ultimate goal in cognitive neuroscience should be to understand, describe, and predict how the human brain processes information and supports behaviour, across experimental trials, within single subjects (Rousselet & Pernet, 2011). Rousselet and colleagues (Pernet et al., 2011; Rousselet & Pernet, 2011) argue cogently in support of a paradigm shift in the analysis of ERP data, one in which we recognize that “…the brain is doing its job on each trial of an experiment, and our ultimate goal should be to understand single-trial brain activity, not activity averaged within or across subjects” (Rousselet & Pernet, 2011, p.4). It is no secret that group level analyses are limited in their ability to detect potentially important within subject variability and do not reveal any information about the presence or absence of effects within individuals, nor do they provide details regarding effects at the single trial level. Advancing our understanding of brain-behaviour relationships could, therefore, be augmented by applying additional analytical tools, including robust estimation procedures.

In general these procedures offer an alternative to removing or ignoring potentially important information about variability across trials (e.g., time course of voltage changes), and also allow for the direct analysis of the unique variability that exists within individuals, on an individual-by-individual basis. Thus, serious consideration needs to be given to methods of robust estimation in ERP research in order for this goal to be achieved. In line with this, Howell (2009) has acknowledged that it is
common for trends in statistical application to change and that “… permutation and bootstrapping procedures will take over – the only question is when” (p.660).

**Future Directions**

A richer understanding of controlled attention and self-regulation could be achieved by extending the proposed domain-general model of medial frontal activation. In particular, in future studies I will apply this model to clarify the differences in brain-behaviour associations between healthy individuals and those with dysfunctional self-regulation, such as persons with issues relating to anxiety, avoidance/defensiveness, and threat detection. It is known that individuals with anxiety tend to show hyperactivation of the medial frontal cortex during performance monitoring compared to non-anxious individuals (Hajcak, McDonald, & Simons, 2003; Olvet & Hajcak, 2009; Weinberg, Olvet, & Hajcak, 2010; Weinberg, Riesel, & Hajcak, 2011). In addition, as described by the adaptive control hypothesis, highly anxious individuals show enhanced recruitment of medial frontal regions that are also engaged during bouts of high cognitive load (e.g., following response errors, and during response inhibition; Cavanagh & Shackman, 2015). One possibility would be to focus on attentional bias to threat by using our response cueing task in conjunction with a task that involves presenting noxious stimuli following failed cognitive control (e.g., air puff). This study could assess whether highly anxious individuals show enhanced activation to non-threatening cues that signal the need for cognitive control compared to those that are paired with unpleasant outcomes, and whether this pattern is different in non-anxious controls. In some of our other work we have shown that medial frontal theta following social rejection in the Cyberball paradigm is correlated with individual differences in self-reported ostracism distress (van Noordt et
al., 2015), suggesting that theta oscillations are a useful measure for understanding individual differences in stress. Thus, by applying the methods used in our studies, future research can lead to better understanding of the attentional factors at the individual subject level that differentiate normal from clinical anxiety and how these affect behaviour.

Pharmacological manipulation of the noradrenergic system could also shed light on the neural correlates of anxiety and the role of medial frontal theta in attention control. Some have used fMRI and found that administration of the monoaminergic drug methylphenidate, which is known to affect dopamine and norepinephrine functions in the prefrontal cortex, increased activation of the dorsal ACC and led to improved conscious error awareness (Hester et al., 2012). Others have shown that administration of alpha 2-A adrenoceptor agonist yohimbine increases error-related brain potentials and facilitates adaptive performance monitoring resulting in reduced commission errors (Riba, Rodríguez-Fornells, Morte, Münte, & Barbanoj, 2005). Importantly, these studies could inform other clinical perspectives and help build transdiagnostic models to help identify developmental risk factors for anxiety and stress disorders, as well as assess treatment outcomes that might appear before subjective or behavioural measures demonstrate reliable effects.

Another avenue of research would be to consider the relationship between the robustness of effects and individual differences in behaviour or personality. Considering the likelihood of finding significant differences in evoked responses in tandem with a measure of the strength of the effect would provide even more information about the intra-individual variability in brain function. For example, those who show more reliable
differentiation in their brain responses to error and correct feedback may be more proficient in successfully adjusting their behaviour on subsequent trials, or perhaps individuals who show a greater differentiation between fearful and neutral faces have a greater tendency to exhibit behaviours associated with anxiety. Electrophysiological research with clinical populations can certainly benefit from the application of these analytical techniques, especially in small samples or case studies (e.g., Allen, 2002).
References


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